To the Jacobs Library
College of "P. & S."

Compliments of the
Author

Wm Seaman Bainbridge.

THE CANCER PROBLEM

THE MACMILLAN COMPANY
NEW YORK · BOSTON · CHICAGO
DALLAS · ATLANTA · SAN FRANCISCO

MACMILLAN & CO., LIMITED
LONDON · BOMBAY · CALCUTTA
MELBOURNE

THE MACMILLAN CO. OF CANADA, LTD.
TORONTO

Natives of Kashmir, in characteristic attitudes, using Kangri baskets. One, standing, is wearing a basket next to the abdominal skin. Two, squatting, have baskets between thighs and knees. These natives thus unwittingly furnish data concerning the production of cancer by chronic irritation, changing entirely the relative distribution of cancer of the skin as known in other parts of the world. (Enlarged from the Third Scientific Report, Imperial Cancer Research Fund.)

THE CANCER PROBLEM

BY

WILLIAM SEAMAN BAINBRIDGE
A.M., Sc.D., M.D

PROFESSOR OF SURGERY, NEW YORK POLYCLINIC MEDICAL SCHOOL AND HOSPITAL; SURGEON, AND SECRETARY OF COMMITTEE OF SCIENTIFIC RESEARCH, NEW YORK SKIN AND CANCER HOSPITAL; CONSULTING SURGEON, MANHATTAN STATE HOSPITAL, WARD'S ISLAND; HONORARY PRESIDENT, FIRST INTERNATIONAL CONGRESS FOR THE STUDY OF TUMORS AND CANCERS, HEIDELBERG, 1906

New York
THE MACMILLAN COMPANY
1918

Set up and electrotyped Published October, 1914.
Reprinted September, 1915.

To

The host of patient sufferers who are facing pain and death from cancer; to the men and women who are earnestly striving to discover the cause and cure of the disease; to the noble friends of humanity who are generously aiding in this struggle, this effort to gain light upon the cancer problem is dedicated.

PREFACE

The cancer problem, as it exists to-day, has a much greater significance than that with which the disease itself was invested by those who first fancied a similarity between its local manifestation, the tumor, with its "roots," and the crab, with its claws, and who applied to it the term "cancer," or "crab."

These ancients who studied the disease had no conception of its prospective importance as a problem of far-reaching import to the human race. The deaths from cancer to-day are said to number at least half a million annually among civilized peoples alone. It is also asserted that the disease is increasing with alarming rapidity, and affecting ever younger and younger ages. If these things be true, then we have here a problem which, if not solved, bids fair to exterminate mankind as effectually as some earlier catastrophe wiped out the flying reptilian monsters whose fossil remains afford so much interesting food for speculation to-day. Even if, as is certain, this is too grave a prospect, cancer is nevertheless the one major problem of medicine still defying any real approach to solution, as regards prevention, reliable early diagnosis, or guaranty of permanent cure.

The tumor was thought by early observers to be the manifest effect arising from the "roots" in the body because of some constitutional condition. To-day we know that the exact opposite is true. The tumor is the starting place, and its "roots" are the offshoots by which it sends out "runners" to the contiguous territory, extending further and further, by minute or by manifest passages, far beyond the original confines, until the whole body is invaded.

So, to-day, interest in the "cancer problem" has carried it, by one kind of "runner" or another, into every phase of life. Not only is it a topic for discussion in the operating room and the medical convention, but in the home, in the business office, in the lecture room, and in the hall of legislation. "Is it contagious?" "May it be inherited?" "Is it caused by certain kinds of food?" "Is it influenced by environment?" "Can it be prevented?" "Can it be cured?" These, and many more pointed questions, are being asked by laymen as well as by the profession. How best to answer them, in the light of our present knowledge concerning cancer, is a debatable matter.

Much of the mystery which surrounds cancer, much of the ignorance concerning it, both within and without the medical profession, is due to the chaotic condition of the literature upon the subject. To acquire dependable information concerning any phase of the question entails tedious search through many books, pamphlets and periodicals. To give a clear, concise, comprehensive, and available résumé of the world's work with reference to cancer, its history, distribution, etiology, diagnosis, possibility of prevention, and treatment, together with various minor matters, is a most difficult task.

With the development of the widespread interest in cancer there has arisen a definite need for a book of ready reference, of convenient size, giving in succinct and available form a summary of knowledge concerning the subject. This is needed by the general practitioner, by the specialist, by the intelligent layman, by the lecturer on health matters; in fact, by all who are definitely interested in questions of health maintenance.

In attempting to meet this need, at least in part, the magnitude of the undertaking has been more and more fully realized as the work of collecting and formulating the data has proceeded. It has been necessary to touch upon practically every phase of the cancer problem, to state *theories,* to emphasize *facts,* to review the work and opinions of those who are qualified to speak with authority, and to maintain throughout an attitude of "suspended judgment pending proof."

In addition to this brief consideration of the *essentials* of cancer lore, a bibliography of some of the most important contributions of others has been compiled, in order that the reader who desires to continue the study of cancer in greater detail may do so with increased facility and lessened expenditure of time. Pictures which depict the horrors of cancer are purposely omitted.

No attempt is made to give a complete work on the surgical treatment of malignant neoplasms. It is manifestly impossible, in a volume of the size and scope of this book, to cover the entire field. At a later date perhaps, a second volume, or a second edition of the present volume, may be put forth, giving a thorough digest of surgical technic as applied to cancer.

The many difficulties of the task which this volume represents will be most keenly appreciated by those who are familiar with cancer research, whether in the laboratory, in the operating room, or at the bedside. To the host of coworkers in this field who have generously given their encouragement and advice I extend my sincere thanks. To members of my staff at the New York Skin and Cancer Hospital I am indebted for patient assistance. Particularly do I desire to express appreciation to Dr. J. Douglas Malcolm for the careful searching of records at the hospital for necessary clinical data; to Dr. D. Stuart Dodge Jessup for painstaking pathological work, and to Dr. Worthington Seton Russell for assistance in the electrotherapeutic study of cases. To Dr. Loy McAfee I am indebted for valuable assistance in the arrangement of the subject matter, especially for the bibliography and index. To the publishers for their prompt and efficient execution of their part of the work I wish to express my sincere thanks.

The mystery which to-day obscures the essential cause of cancer may be cleared away to-morrow; the views held at present may of necessity be abandoned in the near future. Until such a fortunate contingent arises, it is sincerely hoped that this contribution to cancer literature may be of interest and profit to many who are, or who may desire to become, students of one of the most important questions of modern medicine—the Cancer Problem.

CONTENTS

SECTION I

History

SECTION II

General Distribution

SECTION III

STATISTICAL CONSIDERATIONS

SECTION IV

ETIOLOGY

SECTION V

Histopathology

SECTION VI

Cancer Research—A Résumé of the World's Work

SECTION VII

CLINICAL COURSE; DIAGNOSIS; POSSIBLE ERRORS IN DIAGNOSIS

SECTION VIII

PROPHYLAXIS

SECTION IX

THE INVESTIGATION OF "CANCER CURES"

SECTION X

NON-SURGICAL TREATMENT

SECTION XI

SURGICAL TREATMENT

SECTION XII

Irremovable Cancer

SECTION XIII

Institutions for the Care of Cancer Patients

SECTION XIV

The Campaign of Education

PLATES

LIST OF ILLUSTRATIONS IN THE TEXT

SECTION III

SECTION IV. CHAPTER I

SECTION VI

THE CANCER PROBLEM

THE CANCER PROBLEM

SECTION I

HISTORY

ANCIENT HISTORY

Abundant historical references lead to the belief that the disease which we now designate as cancer was known to the ancients at least two thousand years ago. They worked without lens or microscope, and hence could determine nothing concerning the minute structure of tumors and the various tissue manifestations with which they confused cancer. Undoubtedly many errors in diagnosis were made, and many diseases now accepted as of non-malignant nature were considered malignant by earlier observers, just as leprosy, which is so familiar to every child who has read the Bible, probably covered many forms of ulcerating sores as well as certain scaly skin diseases, and did not necessarily mean only *the* leprosy of which we speak to-day.

It is not to be wondered at, therefore, that imagination was given full play in the evolution of the elaborate theories of etiology which have marked the development of the cancer problem, as in almost all problems of disease, from insanity to plague; nor is it surprising that the therapeutic history of the disease is one of the most fantastic of any in the annals of medicine and surgery.

In looking back over the records of the past, we find such a diversity of opinions regarding the origin of cancer, that to give a brief catalogue of the various theories would be an unnecessary tax upon the reader's time and patience. This has been done in a very full and able manner by Wolff.[1] The causative factors involved range from the three "humors" of Hippocrates, Celsus, and Galen, through practically all the indi-

[1] Wolff, Jacob.—"Die Lehre von der Krebskrankheit von den ältesten Zeiten bis zur Gegenwart," Jena. Vol. I, 1907. Vol. II, 1911.

vidual tissues of the body, and to a bewildering number and variety of extraneous agencies. Even the mysticism of the past has been invoked to account for this disease, for we are told by van Helmont (1578-1644) that cancer is due to a spiritual being, the *Archæus,* in the stomach and spleen, which must be purified and thus prevented from sending its ferments into the wrong parts.

The earlier theories which engaged scientific attention are briefly considered under the subject of Etiology (Section IV, Chapter I).

Since the beginning of recorded medical history, and doubtless long before, imagination was given full play in the treatment of cancer. The "witch doctor" combined the secrets of the "black art" with the brewing of the "witch's broth," and the unfortunate victim of cancer was given doses of the mixture. Throughout the centuries the sufferer from this disease has been the subject of almost every conceivable form of experimentation. The fields and forests, the apothecary shop and the temple, have been ransacked for some successful means of relief from this intractable malady. Hardly any animal has escaped making its contribution, in hair or hide, tooth or toenail, thymus or thyroid, liver or spleen, in the vain search by man for a means of relief. The hand on the dial has turned many times to the same point of effort during the progress of the centuries, and it is possible to find in remote districts to-day the same remedies being used that were employed by "cancer curers" of long ago.

We are told, for example, that the idea that *green frogs* in some way influenced the course of cancer has prevailed for hundreds of years, and still prevails in certain quarters. Bonet, of Geneva, in 1682, gave a prescription for an ointment made of green frogs. In the "Kook-Koeck en Recepte Boek," by E. J. Dijkman, published in Cape Colony, eighth edition, 1905, occurs the following interesting item (Trans. J. Muir): "An example of a woman who had cancer of the breast, which was already so severe that eight holes had been eaten into it, and who recovered through the following expedient: She took eight frogs applied to the breast in a muslin bag, which attached themselves instantly thereto as firmly as leeches. When they had sucked to repletion, they dropped off in violent convulsions without the sucking causing pain. This was repeated until 20 frogs were used, which all from time to time, sucked until they died. And the breast was not only cured, but returned again to its normal size absolutely."

Fabricius Hildanus, of Hilden near Cologne (1560-1634), is said to have asserted from certain experience[1] that the following is admirable in curing "ulcerous cankers." The receipt for the water is as follows: "Take suckling Puppies, put them in Wine, and distill it half off *in Balneo;* then take the puppies out, and boil them in a sufficient quantity of Golden-Rod Water, or common Water with Golden-Rod in it; when the Decoction is made, add the Water that was distilled off the young Dogs and boil them together till the flesh comes from the Bones. Then distill them all *in Balneo.* Keep the Water for use. Wet dry clothes or rags in this, and apply it to the ulcerous *carcinoma.* For from certain Experience it heals the sore by cleansing and drying."

The liver of a tortoise "laid on the cancer and used continuously" is a Cape Colony remedy in the "Kook-Koeck en Recepte Boek."

Plunket, a famous "cancer curer" of the eighteenth century in England, used a paste of crow's feet, dog fennel, sulphur, and arsenic. The popularity of this paste is said to have suffered a severe setback when, according to report, it caused the death of Lord Bolingbroke (Henry St. John Vincent), in 1751. Arsenic, which was the base of this, as well as of many other pastes, continues to play an important rôle in the medical treatment of cancer.

John Muir,[2] M.D., District Surgeon, Sterkstroom, South Africa, gives an interesting account of the various "cures" and "curers" of South Africa. Of the herbal remedies the best known is the "cancer bush," or "kanker boschje," the *Sutherlandia frutescens R. Br.,* order *Leguminosae.* An infusion is made of the bark and leaves, and a cupful of this is taken three times a day. As an external application, the oil which accumulates in the pipe of a dagga smoker is used by the inhabitants. In some instances cancer was claimed to have been cured in three days by this "wonderful remedy," which is still in use in South Africa.

The list of non-surgical measures which have been employed in the treatment of cancer embraces hundreds of mineral, vegetable, physical, and animal products, which it would be profitless to detail, or even to catalogue. Many of these are considered in other sections.

The history of the surgical treatment of cancer assumed rational proportions at a much earlier date than did the non-

[1] "A Medico-Literary Causerie. Cancer Curers," *Practitioner,* April, 1899, p. 518.

[2] Muir, John.—"The Cancer Curer in South Africa," *South Africa Medical Record,* January, 1906, p. 5.

surgical. As far back as 2000 B.C., in the writings of ancient India, are to be found directions for the removal of cancerous growths. Radical excision has been advocated for centuries, but it is only within comparatively recent years, or since surgeons have come to understand the histopathology of cancer, that surgical technic has developed to such a degree of perfection as to enable one to say with assurance that it is possible to effect a cure of the disease by means of surgical intervention.

It has been said that more has been accomplished in the study of cancer during the past fifteen years, or since the initiation of modern cancer research, than during the preceding fifteen hundred years.

Such an enormous volume of literature has accumulated on the subject of the origin, development, nature, and treatment of cancer, that to give merely a chronological review of the history of the disease would fill more than one volume of this size. We must content ourselves, therefore, with a bibliography of the early history, devoting more detailed consideration to that later period which covers the era of scientific cancer research.

HISTORY OF MODERN CANCER RESEARCH

THE INFLUENCE UPON CANCER RESEARCH OF THE CAMPAIGN AGAINST TUBERCULOSIS

The renewed activity in the investigation of cancer, which has characterized the past fifteen years, is directly traceable to the success attendant upon the organized campaign against tuberculosis. This campaign was initiated, at an international conference held in Berlin, in 1902, by the founding of the "International Anti-tuberculosis Association." Since that time eleven such conferences have been held.

Inasmuch as the cause of tuberculosis was known, it was possible to proceed to the practical work, and to set in motion measures for the suppression or prevention of that disease. The movement speedily spread throughout the civilized world. Nursing homes, originally established in Belgium, were set up also in France and Germany. The rapid progress of the campaign is illustrated by the fact that the 18 modest hospitals for tuberculous out-patients founded in Germany in 1903, paved the way for the 819 nursing institutions existing in that country in 1913. At the same time and in the same country there were 147 sanatoria, with 15,278 beds; 103 institutions with more than 9,000 beds for children threatened with tuberculosis; 114 forest sanatoria, and 17 forest schools. In addition to all this, special tuberculosis wings—rather than sanatoria—were provided in 1913 in connection with 200 general hospitals.

The great success of the movement against tuberculosis has nowhere been more strikingly evident than in New York City. It is not within the scope of this volume, however, to dwell upon the success of the tuberculosis movement, further than to show how it preceded the revival of interest in the cancer problem, and how, in many instances, it actually determined the nature of the organization and the machinery with which a similar campaign against the latter disease was inaugurated almost simultaneously in America, England, and Germany.

NEW YORK THE FIRST TO ESTABLISH A STATE INSTITUTION DEVOTED EXCLUSIVELY TO THE STUDY OF MALIGNANT DISEASE

In America the inception of the movement for the study of cancer was largely due to the late Professor Roswell Park,[1] who, in 1899, described its beginning as follows:

"Lastly, let me invite special attention to work recently done and projected in New York State. Last year, as the result of persistent efforts on the part of a number of men—both professional and laymen, both in and out of the legislature—the legislature of New York appropriated a small sum for the purpose of 'equipping and maintaining a laboratory' devoted to this kind of research. The money was placed at the disposal of the Medical Department of the University of Buffalo, which seems to be located in a region where cancer is more prevalent than in any other part of the United States. The laboratory was at once instituted and put into operation, the writer of this paper being made its director; and the pathological work was soon placed in charge of Dr. H. R. Gaylord. The equipment of the laboratory is of the very best, and the personnel of its working staff admirably adapted to the work in hand. The primary object of this institution is a determination, if possible, of the nature of the disease; secondary to that, of course, being whatever may be accomplished for its medication and cure. The heartiest coöperation of the profession has been publicly invited, and already, in many instances, obtained. The closest relation exists between the laboratory itself and the clinical opportunities which the University affords, so that by this means there may be the most careful study carried on at

[1] Park, Roswell.—"A Further Inquiry into the Frequency and Nature of Cancer," *The Practitioner*, Vol. 62, April, 1899, p. 385.

the same time of the patient himself and of the specimen removed. The work, so far as projected, includes everything that may be done in the way of clinical study of cases, especially those which are under the personal observation of members of the laboratory staff, a most careful study of the pathological and histological elements found in every fresh specimen removed, a carefully conducted bacteriological examination, with systematic endeavor to cultivate in every known culture medium whatever living parasites may be obtained. As soon as means and space are afforded it is intended to conduct also most minute investigations into physiological chemistry, including chemical and spectroscopic examinations of all the fluids, chemical analysis of secretions, etc. . . . So soon, also, as the State places sufficient means at command it is intended to institute a series of examinations of whatever specimens may be sent us, just as at present in various city laboratories suspected sputum or exudate are examined for the determination of diphtheria, tuberculosis, etc."

This laboratory at Buffalo was the first to be devoted exclusively to the investigation of cancer. It was definitely taken over by the State in 1901, and has since been known as the Cancer Laboratory of the New York State Board of Health. Subsequently it has been housed at the Gratwick Research Laboratory, of the University of Buffalo.

On November 1, 1913, the Research Hospital of the State Institute for the Study of Malignant Disease, was formally opened. Ewing,[1] who made the address on this occasion, thus pointed out its significance—"When a State legislature commits itself to clinical cancer research and devotes public funds to this purpose, it establishes important precedents."

CANCER COMMISSION OF THE HARVARD UNIVERSITY

The surgical department of the Harvard Medical School organized the above body of investigators in 1899. The Commission owes its existence to the generosity of the late Caroline Brewer Croft, and the work has been continued in the Medical School, especially in the department of surgery, by means of this gift and other sums contributed more recently to the cause of cancer research. For twelve years the work was largely restricted to the laboratory study of cancer, the investigations being conducted in the laboratories of the Harvard Medical School and at the Massachusetts General Hospital. The lab-

[1] Ewing, James.—"The Cancer Research Hospital," *N. Y. Med. Jour.*, December 27, 1913, p. 1241.

oratories of the Medical School and of the different science departments of Harvard University are still utilized for the laboratory studies. Since April, 1912, however, the clinical researches have been made in the Collis P. Huntington Memorial Hospital, endowed by Mrs. Huntington.

The aim of the hospital "is the study of special problems with the view of adding to the knowledge of the natural history and the rational treatment of tumors, and also to be of public service in affording means for early diagnosis and in carrying out treatment or giving advice regarding therapeutic measures."

"Another aspect of the work of the Huntington Hospital, of less value to the world at large, but of incalculable benefit to the individual, is the opportunity offered of supplying modern hospital care to the inoperable or recurrent cases of cancer for which other hospitals in the community have no place."

The hospital provides accommodations for twenty-five in-patients. Out-patients are received at stated hours.

An important part of the work of the institution involves the keeping of complete and accurate clinical and pathological records of all cases.

Dr. E. E. Tyzzer, Assistant Professor of Pathology, is Director of the Cancer Commission, and Dr. Thomas Ordway, Instructor in Medicine, is Physician in Charge of the Huntington Hospital.

CANCER RESEARCH IN GERMANY

In Germany, as in the United States, the movement was inaugurated on the basis of cancer being infective. Professor von Leyden and Professor George Meyer, the interest and influence of Professor Kirchner having been obtained, called a meeting, which was held at the Kultusministerium, Berlin, on February 18, 1900. It was attended by ten representative persons who constituted themselves into "Die Comité für Krebsforschung" (The Committee for Cancer Research). Preparations already made enabled the Committee, with Government assistance, to immediately advance, on October 15, 1900, to the taking of a census of all cases of cancer in Germany. This proceeding, and many other steps taken or advocated by this Committee, were determined, as in the case of Roswell Park in America, by the belief that cancer is an infective disease closely analogous to tuberculosis. At the inaugural meeting mentioned, Professor Kirchner was able to announce with the authority of the Kultus Minister—the famous Althoff—that the Government would assist, because "Since a parasitic etiology is supposed, which view the speaker also inclined to, there is the possibility of seriously considering the prevention of this disease. Because it is the duty of the State to take its share in the suppression of avoidable diseases, there can be no doubt that the State officials will participate. The Kultus Minister, and the Directors of the Departments for Education and Medicine, express their lively interest in the matter. The Director Althoff is prevented from being present by official business. Geheimrat Förster, who is unfortunately prevented from being present, is willingly ready to collaborate."

Thus was inaugurated a scheme which has given rise to wide discussion and controversy, not only in Germany but practically throughout the world, because the enthusiasm of this band of public-spirited men speedily attracted followers in Europe and America. The Committee issued the *Zeitschrift für Krebsforschung,* and in other ways stimuli were ever emanating from Berlin to encourage those in other countries to imitate their example by founding committees and taking cancer censuses. The addition, in 1900-1, of a department for cancer to the Royal Institute of Experimental Therapeutics, Frankfort-on-Main, arose out of the influence which this Committee exerted on the Government authorities, as did also the provision, under von Leyden, for special wards and laboratories for cancer in the famous Berlin hospital, The Charité.

Throughout Germany there have been formed local committees in the large towns and in almost all of the federated states. There has been an organized effort to educate the public in the early symptoms of cancer, and a list has been issued recently of institutions which will undertake the microscopical examination of growths, as well as of dispensaries where advice may be sought.

INTERNATIONAL ASSOCIATION FOR CANCER RESEARCH

Out of the efforts of those who had participated in different countries, in founding societies and in their affiliation with the Berlin Committee, there grew up the International Association for Cancer Research, which has had a checkered career. It was inaugurated with enthusiasm at Heidelberg at the opening ceremony of Czerny's Institute, in 1906, when a first International Conference was held. A second Conference was held in Paris, in 1910. This assumed the dimensions of an International Congress, attended by government plenipotentiaries from twenty-three countries; but internal dissensions, arising out of questions of organization, policy, office bearers, and the seat of the permanent secretarial bureau, were apparent. England and Norway persisted in refusing to join the International Association, and France subsequently withdrew from membership. A third Conference, held in Brussels, in 1913, attained to nothing like the same proportions, and attracted little attention. A fourth Conference is foreshadowed in Denmark, in 1916.

From the outset the proceedings of the Cancer Committee met with criticism on the part of the many famous pathologists in Germany who did not care to associate themselves with a policy and proceedings based upon the foregone conclusion that cancer is a parasitic disease. All of them, with the exception of von Hansemann, held aloof, and there were at least two or three notable disclaimers of any share in the responsibility for the views expressed on behalf of the Committee. The taking of a cancer census (in 1902-3) also speedily met with Bashford's criticism. He maintained that it would fulfil no useful purpose in England, and that it should not be imitated in that country, claiming that it was unsound statistically and a needless expenditure of money.

The domestic difficulties of the German Committee naturally extended to the international relationships it attempted to establish. The policy originally laid down was persisted in, unfortunately, with great obstinacy. Had the views of the Committee and its proceedings been made more consonant with what is actually established, it is possible that minor difficulties of organization would have been overcome through the association of other and more numerous representative men, and that a truly representative international association would have been formed. Bashford,[1] who throughout had been the chief spokesman of those opposed to the policy originally pursued by the German Cancer Committee, and to the taking of cancer censuses, plainly restated this position at Paris in 1910.

The *British Medical Journal*,[2] commenting editorially upon the proceedings of the second conference, said:

"In Great Britain they had not a society or committee modeled upon the lines of those affiliated with the International Association, and Dr. Bashford explained that as he was there as the representative of the British Government at the invitation of the French Foreign Office, therefore he was not present as an actual member of the International Association, but

[1] Bashford, E. F.—*Verhandlung des Komitees für Krebsforschung*, Heft III, 1903-4, reprinted from *Deut. med. Woch.*, 1904; First Annual Report Imperial Cancer Research Fund, 1903; Second Scientific Report Imperial Cancer Research Fund, Part I, 1905; etc.

[2] October 22, 1910, p. 1266.

rather as a guest of the French Association. As was well known to his fellow delegates, Great Britain had hitherto held aloof from membership of the International Association. That abstention implied no unwillingness to collaborate, practically, with other nations; on the contrary, it was common knowledge how materially British investigators had assisted their foreign colleagues. The abstention of Great Britain from affiliation with the International Association had no political significance whatsoever, no matter what might have been inferred to the contrary; it was based upon purely scientific grounds only. The presence of an official representative of the British Government was due to the importance attached in all quarters, from the highest to the lowest, to the study of cancer in England, and was, on the one hand, an official recognition of the success with which it had been organized in Great Britain by a number of institutions in addition to the Imperial Cancer Research Fund, of which he (Dr. Bashford) had the privilege to be the Director. On the other hand, the presence of an official representative of the British Government was evidence of the interest of all in England in the proceedings of the International Association, and, in particular, in the proceedings of this Second International Conference. Although not at present a member of the International Association—a fact which he felt bound to emphasize—Dr. Bashford stated that he esteemed it a high honour, a privilege, and a pleasure to be the guest of the French Association; in previous years he had entertained the same sentiments when he had been the guest of the German Association in Berlin and in Heidelberg.

"Although in England they inclined to the belief that the present was rather a time for work—much work—in the hope of advancing knowledge of the disease of which they knew practically nothing, and could do little or nothing to prevent, rather than a time for the holding of congresses, which they thought were premature, since they had nothing revolutionary to discuss or to agree upon, still such a conference as the present might fulfil—indeed, his presence proved that he hoped it would fulfil—a useful purpose."

An interesting exchange of views occurred at the closing ceremony. The President, von Czerny, made a direct appeal to Dr. Bashford to use his influence to obtain the adhesion of Great Britain to the International Association.

In replying to this appeal, Dr. Bashford[1] "assured his hearers that his presence attested to the fact that in England they had no objection, in principle, to such conferences, pro-

[1] Editorial, *Brit. Med. Jour., loc. cit.*, p. 1268.

vided they fulfilled a useful purpose, nor had they the least objection to an international association for the study of cancer, provided its international character was assured, and it was the outward expression of a workable, practicable scheme of collaboration. Speaking as the Director of the Imperial Cancer Research Fund, Dr. Bashford said that he need hardly remind them how substantially that institution had endeavoured to support foreign workers, great and small, and in many countries, by distribution of material and other means, as well as by receiving them as guests in its laboratories. This had seemed to them international collaboration of a practical and useful kind. Addressing the more prominent German delegates by name, and speaking in German, Dr. Bashford assured them how highly he valued the foreign membership of the German Committee and his intercourse with its members. Having expressed the honour and the pleasure it had been to him to be again associated in Paris with his German colleagues, he congratulated von Czerny on the fruitful result of ideas first mooted at the opening of his Cancer Institute in Heidelberg in 1906, from which had sprung this second, larger, and successful international conference."

When, if ever, the inner history of the various moves in this controversy comes to be made public, it will be found how steadfastly one man withstood the influences brought to bear, in favor of what he held—and as the course of events has shown, rightly held—was a mere scheme on paper. Even questions addressed to the Prime Minister in the British House of Commons, and even a petition presented to King Edward VII. during his visit to Berlin, did not alter the conclusion come to, that the cause of the investigation of cancer would be better advanced by other methods than those advocated by the Berlin Committee. Unfortunately, the hopes which Czerny held out, that the objections would be removed, have not been realized. England and Norway still stand aloof, France has withdrawn, and the adhesion of many other countries, like Greece, Persia, Argentina, Peru, Bolivia, Turkey, and China, has little scientific or practical value.

CANCER RESEARCH IN ENGLAND

In England, during a series of years, many eminent surgeons had repeatedly drawn attention to what they held was an alarming increase of cancer, calling for urgent investigation; but the new era in endeavors to probe the mysteries of cancer may be dated from April, 1899, when Malcolm Morris—now

Sir Malcolm Morris—issued a special number of *The Practitioner,*[1] of which journal he was then editor.

"The Editor wishes it to be clearly understood," he said in the editorial preface to this number, "that he has no idea of starting a movement for the suppression of cancer such as has been initiated with good prospect of success in regard to tuberculosis. In the present state of our knowledge the efforts of an association for the prevention of cancer would be as purposeless and as futile as the wanderings of Don Quixote in search of chivalrous adventure. And we should be as poorly equipped for such a campaign as the knight of La Mancha with his pasteboard helmet and his bareboned charger. The movement for the prevention of tuberculosis finds its justification in the reasonable hope there is of success, and this hope lies in the fact that the cause of the disease is positively known, and the means of counteracting its operations are in our hands. The case is altogether different as regards cancer. Its cause is still hidden, or at least too uncertain to be treated, in the practical sphere, otherwise than as an unknown quantity. Some of the best investigators have for years past been striving to wrest this secret from Nature. But life is short and the labour needed for the solution of the problem is long and arduous. If a collective investigation of the ætiology of cancer could be organized on a sufficiently large scale, the prospect of ultimate success would be greatly increased. By 'collective investigation' is not meant the sending out broadcast of schedules of questions, the answers to which are dealt with by a committee which endeavours to extract a kind of essence from the mass. Information collected in this manner may be of some value from the purely statistical point of view, but it is worthless for the elucidation of a pathological problem. What appears to be required is the formation of a band of scientific experts scattered through a number of laboratories in different parts of the world, all in touch with each other. The work should be organized as astronomical research is, each group being at once informed of any observation made elsewhere, so that it may be tested, and of any new line of research being opened, so that it may be followed up. There is too much individualism in scientific work, and the result is not only waste of power, but actual loss of knowledge, which is allowed to die with its discoverer because he could not get a hearing for it, or because it failed to find favour in the eyes of some superior person. With a proper organization of research on definite lines by a number of investigators working together to a definite end, there would

[1] *The Practitioner,* April, 1899, Vol. LXII, p. 362.

be little or no leakage, and success would be merely a matter of time."

Conspicuous examples of cancer research organizations in England are found in the Cancer Department of the Middlesex Hospital, which combines the clinical with the laboratory investigation, and the Imperial Cancer Research Fund, which confines its work to the laboratory and statistical study of the disease.

Because these institutions represent distinct types they are discussed somewhat more at length than are other research organizations.

CANCER RESEARCH LABORATORIES, MIDDLESEX HOSPITAL

Independently of the movement thus initiated by Sir Malcolm Morris, steps were being taken to have the Cancer Wards of the Middlesex Hospital associated with a special investigation department.

From 1792 up to the present day, the Cancer Department of the Middlesex Hospital, London, has remained a distinctive feature of the establishment, affording not only a refuge for a vast number of those suffering from cancer, but also opportunity for investigation and for the testing of alleged remedies. The objects of the donor, Mr. Whitbread, were therefore twofold—the relief of suffering and the investigation of the disease. Mr. Howard, who acted as intermediary for the benefactor, expressed himself as regards the second object as follows.[1]

"With regard to the second object, namely, the investigation of the disease, Lord Bacon has observed that medical men should make themselves proficients in physic by studying one disease at a time. It is an opinion worthy of so great a man; it was particularly adopted by the late Mr. Pott, and by him recommended to all students in surgery.

"By confining one or more wards to cancer only, the attention of pupils and others will be directed very strictly to the study of this disease. They will see facts as they arise in the aggregate from a large number of patients; new lights will appear, and new discoveries will probably be made.

" 'I have often thought,' says Dr. Sydenham, 'that if I knew accurately the natural history of any disease, I should never be at a loss for a proper method of treating it'; and the wonderful

[1] Coupland, Sidney.—"The Cancer Charity of the Middlesex Hospital, 1792-1902." Reports from the Cancer Research Laboratories of the Middlesex Hospital, Vol. I, London, 1902, p. 1.

improvements he made in science by his great attention to the natural history of diseases, and the effects of medicine upon them, have been justly admired by practitioners of every country. (*Vide* the Preface to Dr. Sydenham's "Observations on the History and Cure of Acute Diseases.")

"The natural history of cancers, although a common disease in the enlarged comprehensive sense in which this great man understood the natural history of diseases, is but little known. I would therefore, in order to improve a subject on which a successful practice greatly depends, propose that a faithful account of the history and circumstances of every case be kept: its antecedents and consequences should be marked, the effects of medicine and of operations, when necessary, noted, together with all the collateral helps to be gained by an inquiry into constitutional habits and diseases not strictly cancerous, but probably connected with it. This examination may be made by a medical gentleman of the hospital with the patient before him, his notes to be corrected by himself, and kept as a record of the history and circumstances of each case, to be recurred to, as an authority, by any intelligent or scientific person. A copy of these notes may be kept, fairly written, for general inspection; and if anything extraordinary or worthy of more particular notice arise from these sources, let the circumstances be published to the world at large.

"By an institution comprehending the two objects now pointed out, I have a hope not only that the diseased, but that practitioners in general may be benefited, that much useful knowledge may be disseminated, and that we may, in no great length of time, be furnished with documents on the disease and cure much more authentic than any we are at this time in possession of. It is a very important subject of inquiry, equally interesting to the rich and independent part of mankind as to the poor; and if such an institution be fairly set on foot, it cannot fail of producing beneficial consequences to all descriptions of persons labouring under this dreadful malady."

Since the foundation of the Cancer Ward, in 1792, various extensions and improvements have been undertaken, and in 1896 a more ambitious nature was given to the establishment when plans for a new cancer wing were approved. The new cancer wing was approaching completion in February, 1899, and, not unmindful of the wishes of the original founder, at a meeting of the Weekly Board, on February 7, 1899, "the Chairman having made a statement, as a preliminary, in view of the opening of the New Wing for Female Cancer Patients, and more particularly in regard to its medical supervision for carrying out the wishes of the original founders of the Cancer Wards, it was, after some discussion, moved by Sir Arthur Watson, seconded by the Hon. Spencer Lyttleton, and resolved unanimously:

"That the Weekly Board of Governors are of opinion that, in the arrangements to be made for the medical supervision of the new Female Cancer Wards, endeavours should be made to give effect to the wishes of the original founders, which are expressed in the conditions submitted by the late Samuel Whitbread, Esq., in 1791, in the following terms, viz.: 'The relief of persons affected with Cancer, and the investigation of a complaint which, though extremely common, is, both with regard to its natural history and cure, but imperfectly known'; and likewise laid down in the will of the late Mrs. Alithea Maria Stafford, as follows, viz.: 'Curing persons affected with Cancer, and of investigating and promoting our general knowledge of treating that dreadful disorder.' And the Board would be glad if the Medical Committee would consider how this could best be done. The enhanced facilities for pathological and bacteriological study in the Hospital is, they consider, an additional reason why some practical steps should be taken in this direction.

"In establishing the Cancer Research Laboratories the Governors of The Middlesex Hospital have not only been faithful to the trust confided to them, but they have set an example to others similarly engaged in the warfare against disease. They have perceived that the only sure foundation upon which successful treatment can be based is that of knowledge of the nature and causes of diseases. In such investigations as can alone be carried on into the difficult and complex problems of cancerous affections, it may be long before any decided practical result can be attained. But the labour will not be thrown away. Every additional fact, however small, will contribute to the better understanding of the conditions under which such diseases arise and the manner in which they spread. That in due time such knowledge will be the means of directing us where to look for the means of checking and preventing cancer there can be little doubt. Such a consummation will, however, only be attained by the exercise of unwearied patience and assiduity by those engaged in the task." [1]

At a later date Dr. Lazarus-Barlow became Director of The Middlesex Hospital Cancer Investigation Department, which, in 1909, underwent an important extension and reorganization in consequence of the Barnato Bequest. The investigations

[1] Coupland, *loc. cit.*, p. 34.

under Dr. Lazarus-Barlow's leadership have become closely identified with the study of radium as a possible constituent of tumors as well as a therapeutic agent.

IMPERIAL CANCER RESEARCH FUND

In the First Report from the Cancer Research Laboratories of The Middlesex Hospital, Dr. Sidney Coupland gives an interesting and valuable summary of what had been done up to 1902, with a succinct statement of the object of the work. This summary ends as follows:[1] "Finally, the present year (1902) has seen the formation in this country [England], under the auspices of the Royal College of Physicians of London and the Royal College of Surgeons of England, of what may be regarded as a National Committee for the promotion of Cancer Research."

This organization, originally known as the Cancer Research Fund, in recognition of investigations which had developed throughout the British Dominions, had the title of Imperial Cancer Research Fund bestowed upon it in July, 1904, by King Edward.

The development of the work, whose inception dates from a conversation between a private gentleman and a member of the Council of the Royal College of Surgeons of England, in 1901, was placed in control of the Royal College of Physicians and Surgeons.

A General Committee was appointed by these bodies to formulate a scheme of research, and as the result of their deliberations, extending over many meetings, a plan was approved on July 4, 1902.

As soon as the sum of £30,000 was in hand the two Royal Colleges consented to inaugurate the investigations, with the full understanding that with so small a sum it would be necessary to spend the capital and to limit the scope of the work.

The organization and objects of the scheme have been officially described,[2] in part, as follows:

In order to promote investigations into all matters connected with or bearing on the causes, prevention, and treatment of cancer and malignant disease, steps shall be taken:

"1. To provide, extend, equip, and maintain laboratories to be devoted to cancer research.

[1] *Loc. cit.*, p. 38.
[2] *Lancet*, July 12, 1902, p. 101.

"2. To encourage researches on the subject of cancer within the United Kingdom or in the British Dominions beyond the seas.

"3. To assist in the development of cancer research, in various hospitals and institutions approved by the executive committee.

"4. And generally to provide means for systematic investigation into the causes, prevention, and treatment of cancer.

"Should the objects of the Fund be attained by the discovery of the cause and nature of cancer, and of an effective method of treatment, the Royal Colleges, with the consent of the Trustees, shall be empowered to utilize the Fund, (a) for equipping with the necessities for such treatment such hospitals as they may select, or (b) for forwarding research into other diseases."

It was decided that the affairs of the Fund be administered by the president, vice-presidents, five trustees, a general committee, an executive committee, a working and consultative staff.

The investigations were set going in October, 1902, on the basis of a draft scheme for inquiring into the nature, cause, prevention, and treatment of cancer, drawn up by Dr. E. F. Bashford previous to his appointment as General Superintendent of Research. A few months later Dr. Bashford was also elected director of the laboratory. This scheme is reprinted from the Third Scientific Report of the Imperial Cancer Research Fund, 1908, p. 441.

"1. General Nature of the Enquiry and General Organisation.

"*Scope.*

"The term 'Cancer' must be taken to include all malignant new growths, and this conception must be extended to similar diseases in animals, both for studying the subject in them, and in relation to the possibility of transmission to man.

"*Character Constituting Malignancy and Spread.*

"The investigation must further include the conditions favourable to spread in the body and the other features of malignancy, since these constitute the serious aspect of cancer as distinct from innocent growths. Any change which would prevent the acquisition of malignancy, or which would hinder such spread, would be of very great value.

"*Statistics as to Incidence. General Causes.*

"The enquiry should include the compilation of accurate statistics bearing on all the conceivable conditions possibly associated with the incidence of the disease.

"*The Possibility of Different Causation in Different Groups; Separation of Special Groups, some possibly Parasitic.*

"The study of all new growths in order to classify them, and to distinguish the various forms which at present may be grouped together as malignant growths is important. It might thus be possible to eliminate some types which may be found to be of definite, and possibly of very diverse parasitic origin. This will constitute an important feature of the work to be done.

"*Experimental Production of 'Cancer.'*

"It will be necessary to attempt to produce new growths in various ways, or to attempt so to modify non-malignant growths that they become malignant.

"*Bio-chemical and Physiological, possibly including Therapeutic Substances.*

"Investigations along modern bio-chemical lines, with consideration of the conceivable production of cytolytic, agglutinative, antagonistic, perhaps therapeutic sera, and the possible occurrence and antagonistic nature of internal secretions, etc., will demand very serious attention.

"The organization will consist of:

"(1) A central bureau and laboratory for general direction of the undertaking, for study, research, control of work being done and of the results obtained elsewhere, and for the summarising of results and the interpretation of statistical investigations by those working there.

"(2) Associated workers carrying on special parts of the investigation in their own laboratories or hospitals, etc. There would thus be an attempt to utilise so far as possible existing laboratories, and also skilled workers, who occupy other important positions.

"(3) Other persons from whom statistics might be collected, etc.

"The ultimate greater development of the experimental side of the enquiry being borne in mind, the control work might be begun by classifying all that is grouped under the term malignant disease, and by collecting statistics.

"At the outset two or three rooms giving accommodations for the director, one or two good secretarial assistants, and two or three assistants skilled in microscopical work would be required.

"At a subsequent date the investigation will in all probability require much more extensive laboratory accommodations, and it will be necessary to obtain some place where animals can be bred and kept, and probably a farm will be required.

"Of the skilled assistants, one should if possible be a trained veterinary surgeon who, apart from his special duties in connection with the important veterinary aspects of the research, would at a later date be invaluable in regard to supervision of animals destined for research purposes.

"In an enquiry which may ultimately require the keeping of many animals, both of the larger forms, *e. g.,* horses, anthropoid apes, etc., proper attention to the hygiene of the animals would be essential; apart from the experimental importance of being able to exclude previous infection, ultimately a proper farm with efficient means for isolation and perhaps for the breeding of animals would be necessary.

"A second assistant should be especially detailed to assist in the bio-chemical researches, and should have had a proper chemical training, if possible; also a training in physiological chemistry. A third assistant should preferably be a man skilled in zoölogical and general biological enquiry. All assistants should be skilled in microscopical and general histological technique.

"At a later date a larger expert staff will probably be found necessary. In the compilation of statistics the services of a trained actuary would be almost essential for a time.

"The enquiry must start at selected points and be allowed to develop itself in the hands of those conducting it along those lines which the experience accumulated, will in natural course dictate. The proceedings must therefore be cautious, and conducted on the very widest basis. At present we possess no knowledge which justifies limiting the enquiry in any special direction, but no reasonable line of special enquiry should be discouraged.

"The scope at the outset being so very wide, the work should primarily be directed to attempting to define the field of legitimate enquiry, and within the shortest time possible attempting to focus the efforts on a rational research for the causal factor or factors. This limitation may best be obtained within a reasonable period by following out systematically various lines of enquiry at the same time:—Statistical, histological, chemical; pertaining to cancer in various human races, animals, plants (?), and with consideration of all alleged causes—heredity, race, climate, soil, etc., and also the reputed increase of cancer.

"2. RECOMMENDATIONS BEARING ON SPECIAL LINES OF ENQUIRY WHICH MAY BE DIVIDED INTO STATISTICAL, EXPERIMENTAL, ETC.

"*Statistical.*

"The proper study and interpretation of the returns of the Registrar-General should be augmented by special enquiry directed by the central body, because the special statistics already compiled and commented on, and especially those of the German and Dutch Cancer Committees, and those relating to Massachusetts, have not yet brought to light evidence free from ambiguous interpretation, nor have they the value which presumably would attach to the similar compilation based on the widely divergent races, regions, isolated communities, etc., which would come within the scope of the present enquiry, comprising as it will the whole British Empire.

"The compilation of statistics would have to be conducted along the soundest lines, and with regard to all conditions which may be supposed to favour the occurrence of malignant disease in man and animals.

"Any scheme drawn up should be submitted to a statistical expert for approval.

"A sufficiently extensive statistical enquiry may be expected to lead to the accumulation of facts helping to decide whether any form of disease comprised under the term 'malignant' is communicable from one individual to another. It may further be of help in determining the direction enquiries as to the cause or causes are to take.

"Owing to the time it will take to get together the mass of important evidence, which is waiting to be collected in different parts of the globe, I would suggest that early steps be taken to organise this collection.

"I would divide into two great classes those to be relied upon for the immediate collection of the information sought, viz., those voluntarily assisting, and those who can be enlisted in the service through the different government offices and various local authorities.

"It will thus be necessary at an early stage to ascertain how far the Local Government Board, India Office, Colonial Office, etc., town and county councils, and other authorities having medical or veterinary officers in their services would be inclined to assist the enquiry.

"Those voluntarily assisting would be essentially the staffs of hospitals and general practitioners. A direct appeal to each institution and individual seems desirable in order to direct attention to the special points on which definite information is wanted.

"To avoid misapprehension, secure uniformity, intelligibility, and ready classification of the information obtained from such divergent sources as isolated Crown colonies, town and county communities, etc., definite questions should be asked. These being intended to elicit from distinct sources, both similar and different kinds of information, it would be necessary to draw up the various subjects of enquiry. In regard to this matter advice might well be sought from the German Cancer Committee, who have already some experience of it.

"In the interval that may elapse before the return of these enquiry forms, arrangements would have to be made for the classification and interpretation of the returns under the combined direction of a trained statistician and a director or other medical official.

"*Importance of Co-operation in Experimental Work.*

"In order to obtain the co-operation of skilled workers who would carry on special parts of the investigation at their own laboratories, etc., it would be necessary to arrange both for grants to them for their expenses, and for honoraria for their work. There are many who might thus be encouraged to assist the enquiry by undertaking special work on suggestions given to them by the central body, *e. g.*, those who wish to use their work for the purpose of a graduation thesis at a University.

"Of course, any work of this nature may be performed in any laboratory, the only condition being that the worker is fully qualified to undertake the work proposed, and that any control or suggestion on the part of the central body would be permitted by the chief of the laboratory in which the work is being done. In order to emphasise this side of the enquiry, circulars would have to be directed to all institutions likely to afford facilities for work of this nature, or, to provide such workers. The importance of central control would have to be emphasised, and the necessity for avoiding undue overlapping brought into prominence.

"Importance of Study of 'Malignancy.'

"The causes of, or changes which may accompany, or be responsible for, spread in the body must be investigated with especial care. The study may indicate the means by which power to spread may be removed, or may point the way to limitations in other directions. In this connection only the emaciation, secondary anæmia, and leukocytosis have received much attention. The not infrequent occurrence of pigmented moles, warts, etc., in albino and other animals seem to offer favourable conditions for a much more extensive investigation into the occurrence of other conceivable phenomena. Thus the possibility of converting innocent conditions into malignant growths may be studied, and the importance of investigating the possible influence of internal secretions, by means of the injection, etc., of emulsions, watery and other extracts, fluids obtained under high pressure, or by means of a gelatine filter under high pressure from malignant growths must not be lost sight of. The study by recent methods, of changes in the serum and other fluids in cases where spread is occurring, or where an 'innocent' tumour has become malignant, with a view to detecting there the presence of anything of the nature of an immune body, in Ehrlich's sense, must receive attention. It is impossible to express any opinion on the likelihood of being able by these means to ascertain the presence of factors which may cause spread, be concomitant with spread, or have really an antagonistic influence on spread.

"Importance of properly controlling all Bio-chemical Enquiries in order to avoid fallacies and all tendency toward their assuming a too speculative nature.

"Owing to the extreme complexity of the experimental methods necessary to this line of enquiry, it could only be carried out under the direction of one familiar with the methods, the manifold fallacies likely to present themselves, and the equally numerous control experiments necessary.

"Granted due attention be paid to the above sources of error, purely hypothetical considerations must for the present suffice to suggest the following lines of enquiry.

"A thorough scrutiny of malignant disease in the light of the knowledge which has been recently acquired in regard to hæmolysis, cytolysis, cytotoxines, immune-bodies, and the mechanism of their action, etc., ought to be undertaken.

"The following special lines of enquiry also suggest themselves:—

"A search should be made for evidence of anything arising pathologically, or experimentally, in consequence of the prolonged irritation of tissues, or the existence of cancerous conditions. Such evidence might be sought for in the existence of anything in the nature of excessive waste products, modified alkalinity of fluids, autolysines, isolysines, etc., such as it may be assumed might possibly stimulate local or general vegetative activity, or give rise to detectable excess, or deficiency of any constituent of cells, or of fluids. Also any evidence of local or general irritation arising from such causes should be sought.

"An endeavour might be made to determine if the chemistry of the normal cell shows any divergence from that of the cancer cell which has developed from it. By means of modern methods applied to the albuminous bodies, ferments, etc., it might be possible to determine any divergence in the nature of the constituents of these cells; the presence or absence of normal or abnormal constituents might be sought for.

"Hofmeister has recently pointed out the large number of distinct ferments contained in any one cell of the liver. It would be interesting to ascertain to what extent these ferments are present in the cells of malignant disease of this organ.

"An enquiry might be instituted to determine if any stimulation of cells can be made to lead to the production in the latter of manifestations of activity with depression of the special function (secretion, motile phenomena, etc.), *i. e.*, without calling forth what is regarded as the special function of the cells stimulated.

"Classification and attempted Experimental Production of 'Cancer'.

"In regard to the attempted experimental production of innocent and malignant new growths in animals, or the possibility of setting up the features of malignancy in benign growths, it may be well to repeat some old experiments, for example, in relation to embolism, etc., where the results obtained may have been vitiated by the conditions under which the experiments were at the time carried out.

"In this connection the possible experimental production of 'Petroleum cancer' and 'Sweeps' cancer' would have to be borne in mind, and experiments carried out on a very wide series of differing species of animals.

"The classification of different forms of cancer, if properly carried out, might lead to the elimination of some forms which may be found to be due to special parasites (as, for example, actinomycosis has been eliminated), and to the separating off of what may be found to be special types, or only seeming cancer. In all investigations of this nature full and detailed histological, chemical, bacterial, or other parasitic investigations must be made and a full history of each case clinically recorded.

"The reputed transplantation of cancer into wound margins ought to be specially enquired into, with a view to the important bearing such an occurrence would have on other transplantation experiments. Such transplantation experiments should only be carried out with regard to the special species of animal in which the original growth occurred, and the special tissue in which it seemed to have had its origin. For all experiments of this nature the importance of the assistance of a trained veterinary man is very evident, for it would be especially necessary to exclude the possibility of previous infection.

"A systematic study of the effects of persistent irritation of different epithelial surfaces in different species of animals might be found to have important bearings. In this category possibly the study of 'Petroleum cancer' and 'Sweeps' cancer' might be placed.

"Those engaged in post-mortem examinations should be encouraged to search systematically for, and record all evidence of incipient or undetected malignant disease. Such an investigation might throw much light on the internal conditions, *e. g.*, in the alimentary canal, which in themselves may perhaps lie long dormant, and in the end become malignant, in the same way as other conditions on the surface of the body are known to do.

"A comparative study of mitosis and vegetative activity would require to be undertaken. Such an investigation would cover not only mitotic and vegetative activity in embryonic and cancer cells, but also that occurring in the cells in benign tumours, and of tissues which have reverted to an embryonic type in processes of repair, and with consideration of that over-production which is an essential feature of repair.

"I would respectfully submit that any such scheme as the foregoing can only be provisional, and has been drawn up in full consciousness of the difference between drawing up a scheme on paper and putting the same into practice. I do not claim that this hastily drawn up scheme is adequate to cover the whole field of enquiry. In conclusion I would point out that the investigation must necessarily follow the lines which accumulated experience will dictate.

"(Signed) E. F. Bashford.

"Edinburgh, October 24, 1902."

Bashford was able to conclude his preface to the Third Report by stating, in 1908, that with the completion of this Report all the points raised in the provisional scheme of inquiry drawn up for the Executive Committee in October, 1902, have been submitted to investigation. He continued: "The important investigations made by workers elsewhere and also by my colleagues in the laboratory since that date, have naturally had much influence on the conduction of the work."

The investigations of the Imperial Cancer Research Fund continue to develop along the wide and numerous paths they have so consistently pursued. A most important aspect of its activities has been the extent to which material, in the form of animals bearing transplantable tumors, has been distributed throughout the world, and the welcome independent investigators have been given to conduct their own work in its laboratories. Associated with Bashford there have been Murray (from the beginning), Cramer, Haaland, Russell, v. Gierke, Da Fano, Woglom, Medigreceanu, Bowen, Copeman, Wake, Compton, Bullock, and others.

OTHER CANCER RESEARCH INSTITUTIONS

The establishment of these larger schemes has naturally been followed by other developments, notably, in 1906, by the foundation of Czerny's Samariterhaus at Heidelberg, to some extent through Czerny's generosity when he resigned the University Chair of Surgery.

A large and well-equipped institute has been added to the Brompton Cancer Hospital, London; and the Royal Cancer Hospital, Glasgow, has a laboratory on a smaller scale. In Moscow, for some years, there has existed the Morosoff Institute. In Dundee a special cancer laboratory was attached for a time to the Royal Infirmary, and similar provision existed for some time in the University of Liverpool.

The Austrian Cancer Committee has equipped a well-appointed chemical laboratory in Vienna; and in Hamburg, Cologne, and Leipsic special laboratories have been or are about to be attached to the large general hospitals.

In Europe the most recent event of importance in this movement has been the opening, in the presence of the Kaiser, of a new Institute for Experimental Therapeutics at Dahlen, Berlin, to be devoted mainly to the investigation of cancer and tuberculosis.

In America, we note as most important, the growth of the Cancer Department of the Rockefeller Institute, the laboratory of the St. Louis Cancer Hospital, and the formation of the Crocker Cancer Fund. In considering all these institutes and laboratories and the workers who have enjoyed their exceptional facilities, it must not be forgotten that individual workers in laboratories elsewhere, for example, Jensen, in Denmark, and Borrel, of the Pasteur Institute, in Paris, have exercised a profound influence on the development of modern cancer research.

George Crocker Special Research Fund at Columbia University.—Among the more recently endowed institutions for cancer research is the George Crocker Fund. This endowment is not only the most important in America, but its capital funds represent the largest sum appropriated anywhere in the world toward the investigation of the disease. While the work of organization has been proceeding, the money available has not been allowed to lie idle. It was decided by those who had the matter in hand "that the money could best be expended by making grants to special workers in the laboratories of the College of Physicians and Surgeons and of the Department of Zoölogy of Columbia, in order that no time might be lost and the money put to immediate use." In 1912 Professor Francis C. Wood was appointed Director, and Dr. William H. Woglom, Assistant Director. A laboratory has been erected and clinical connection will be maintained with St. Luke's Hospital.

The Institute for Cancer Research attached to the Charité Hospital, Berlin, founded in 1902, consisted of the provision of a small number of beds and a small laboratory for experiments on animals. It was originally under the direction of v. Leyden, and with him were associated, among others, F. Blumenthal, L. Michaelis, and C. Lewin. Subsequently, after the death of v. Leyden, Professor George Klemperer became Director, Carl Lewin remaining as Assistant. The laboratory is now housed in a separate building outside the Charité in Luisenstrasse. During v. Leyden's directorship he himself strongly upheld the parasitic hypothesis and sought to utilize the experimental study of the disease in its support. The publications from his Institute were influenced by his views in the cases of both Michaelis and Carl Lewin. Carl Lewin still maintains this outlook on the problem, and Klemperer has also recently committed himself to the view that cancer arises from outside. More recently this Institute has become associated, through Emil Fischer, with the search for some chemical substance having a special affinity for the supposed cancer parasite or for the cancer cell: in other words, it has become associated with the chemotherapy of cancer as inaugurated by von Wassermann.

In *The Royal Prussian Institute for Experimental Therapeutics,* at Frankfort-on-the-Main, under the direction of Professor Ehrlich, there has been a department for cancer investigation since 1901. Associated with Ehrlich originally was Sticker, who worked with the so-called venereal tumors of dogs. Later Apolant has been connected with this Institute, and with Ehrlich has published numerous histological papers on tumors in mice, as well as valuable contributions to the study of immunity. Moreschi, who has also worked here, confined his work mainly to feeding experiments.

Ehrlich's scheme of inquiry appears to be entirely along biological, histological, and cellular lines. He has never given any indication that he agreed with the infective views originally put forward by Sticker during and after the time when he was one of Ehrlich's colleagues. He has, however, given indications that he attaches importance to Cohnheim's germinal rest hypothesis and to the possible influence of constitution.

On the twenty-fifth anniversary of the foundation of the Pasteur Institute, November 15, 1913, Roux gave a résumé of the activities of the Institute. He pointed to the fact that Borrel, who is one of the chiefs of a department there, had consecrated himself especially to the study of cancer, working on the basis that cancer arises from the outside owing to the existence of a cancerous virus. Borrel had been especially impressed by what he regarded as veritable epidemics in certain breeds of mice. Borrel also regarded the virus as being probably conveyed to cells already prepared for its reception in consequence of prolonged irritation. The parasites to which he attached most importance were various forms of worms and the demodex. With Borrel there have been especially associated Haaland and Bridre. Haaland subsequently spent a short time in Ehrlich's Institute, and after a transitory stay in his native country (Norway) was for over three years an Assistant to the Imperial Cancer Research Fund in London, which he left to become Director of the Gade Institute in Bergen.

In Paris there exists the *"Association Française pour l'Étude du Cancer."* The work of the Association has resolved itself largely into the holding of meetings for the reading of papers. It issues the "Bulletin de l'Association Française pour l'Étude du Cancer," and "La Revue du Cancer." The objects of the Association, as set forth in its statutes, are:

1. The carrying out and publication of experiments relative to cancer.

2. The organization of laboratories, dispensaries, hospitals, etc.

3. The granting of honoraria to authors of works worthy of interest.

This Association was also responsible for the organization of the large International Conference held in Paris in 1910.

Czerny's Institute in Heidelberg is an Institute of the University. It is known as the Samariterhaus, in order that patients may not fear entering a *cancer* hospital. It receives cancer patients, and those suspected of suffering from cancer and all other tumors; they are treated according to the best and latest scientific methods. Attached to the hospital are chemical, experimental, and parasitological departments. Von Dungern and von Wasielewski have been successful directors of the laboratories. Associated with them has been Dr. Richard Werner, who has devoted himself particularly to statistical investigations. Czerny's hospital has become mainly identified with attempts to supplement surgery by other means—for example, X-rays and fulguration. Practically all the non-surgical measures which have recently been put forth have been tested in the wards of his hospital, where a combination of treatments has also been given full trial.

In 1912 the *American Association for Cancer Research,* which is affiliated with the International Association for Cancer Research,[1] came into existence. The purpose of the Association is to further the research and spread of the knowledge of cancer. It has held several meetings at which a large number of scientific communications have been made.

COMPARISON OF METHODS OF INVESTIGATION

From the preceding accounts of the beginnings of the more notable efforts in different countries to elucidate the mysteries of cancer, it will have become evident that the methods adopted have been widely divergent.

The German Committee was originally in essence a society for the reading and discussion of papers on cancer, by an assemblage of experts, through whose influence special statistics

[1] At a meeting of the Council of the American Association for Cancer Research, at Toronto, April 9, 1914, it was voted that this association withdraw from its relationship with the International Association for Cancer Research.

on the subject (over and above the national statistics) were compiled, and under the influence of the opinions of the majority of the committee, who held that cancer was an infective disease and should be combated as such. In short, the method employed was that of settling subjects of scientific discussion and regulating the conducts of investigation by a majority vote.

In the case of Roswell Park's scheme for the conduct of the New York State Laboratory, and that of Foulerton for the Middlesex Hospital, the original aim of investigation was frankly declared to be the better utilization of clinical material; and, in the case of the Middlesex Hospital, the possible bearing of some lines of inquiry on the national statistics was not forgotten.

The plan of investigation drawn up by Bashford for the Cancer Research Fund was of much wider scope, and placed the investigation at once upon a wide comparative basis—pathologically, statistically, and experimentally, as regards different races of mankind and animals. If the share which the German Committee had in attaching a cancer department to the Charité in Berlin and to Ehrlich's Institute in Frankfort be excluded, Bashford's is the only one of the larger schemes in which a sharp separation of human patients from the development of the study and experimental investigation of cancer in animals was fully considered and provided for.

INSTITUTIONS WHICH COMBINE CLINICAL AND EXPERIMENTAL WORK

All these schemes have now departed to a great extent from their original form, owing to development along lines of their own, associated with the results which their several plans yielded, together with the influence exerted by the general progress of the investigations. Since their initiation there have sprung up other important centers, such as Czerny's Institute in Heidelberg, the Research Institute of the London Cancer Hospital, and others, in which the attempt is made to combine clinical work on the disease in man with experimental study of cancer in animals. Both the New York State Institute and the Harvard University Commission have added a small amount of special hospital accommodation to their laboratories.

RESEARCH DEPARTMENT, NEW YORK SKIN AND CANCER HOSPITAL

The cancer research work of the New York Skin and Cancer Hospital has been in progress since 1904, when the author first became connected with the institution. It was primarily clinical. As the surgical work rapidly progressed, the immense field for research investigation in connection with it became more and more evident, and it was not long before a well-equipped pathological laboratory, with a skilled pathologist in charge, was added to the cancer department.

The research work was given direction partly in consequence of an offer, through the hospital, of a cash prize to be awarded to anyone who might discover a cure for cancer. Such a volume of "cancer cure" correspondence was precipitated upon the writer, as Secretary to the Research Department, that it soon became evident that there should be, in this country, an institution like the Middlesex Hospital Cancer Department, London, in which proposed agents and methods for the treatment of cancer might be "tried out."

The first definite research work of this character was the trial of the Enzyme method, generally known as the "Trypsin Treatment." This is reviewed briefly in Section IX.

Of this test, the *Lancet,* October 9, 1909, p. 1079, under the caption, "The Enzyme Treatment of Cancer," said: "Undeterred by the discredit into which the methods of some of its exponents had brought the theory, Dr. Wm. Seaman Bainbridge, the author of this report, has fulfilled his undertaking to give the treatment a fair trial, both in operable and in inoperable cases. Many of the patients have been followed to their homes, and nurses provided, after leaving the hospital, while everything possible has been done to make the clinical and pathological observations complete. The list of patients and the account of the results given by Dr. Bainbridge are records of the miserable failure of the treatment, but they are monuments of industry which will be of service in the interests of sufferers from cancer. . . . The negative result of the investigation is to be regretted, but the courageous persistence in its conduct in the face of discouragement, and the care with which the tests have been carried out in all particulars by Dr. Bainbridge for the New York Skin and Cancer Hospital, may serve as a model to other institutions."

The final recognition of the useful object fulfilled by the "Trypsin Test," made it possible, financially, to launch the Research Department on a really creditable basis. At the present time six Research Fellows are giving their services, in full or in part, to the work, with fair remuneration.

In addition to the treatment of cancer by the usual surgical measures, the work of the Research Department of the New York Skin and Cancer Hospital is fourfold:

(1) The care of advanced cases—those which are usually considered "inoperable." In a large proportion of instances these patients represent the end-results of treatment by various so-called "cures," and many more have been the subjects of one or more surgical procedures. They may all be said to be hopeless, so far as cure is concerned, but much may yet be done to relieve suffering, to prolong life, and to make their remaining days comfortable. Not only are the patients themselves often cared for in a more satisfactory manner than is possible in their homes, but their friends and relations are spared many of the distressing circumstances attendant upon the care of victims of cancer in the last stages.

(2) The clinical application of surgical and non-surgical methods of treatment which, from time to time, are proposed, and which seem to warrant a thorough trial. This includes the various bio-therapeutic agents.

Among the various methods of treatment which have been and are being efficiently tested, may be mentioned the employment of Arterial Ligation in the treatment of advanced cancer (see Section XI, Chapter 2), Fulguration (de Keating-Hart), Electrocoagulation (Doyen), Thermopenetration (Nagelschmidt), and Thermoradiotherapy (de Keating-Hart). (See Section X, Chapter 2.)

(3) The careful study of the blood, urine, and other body-fluids of cancer patients, and of the structure and classification of the neoplasms removed. Each case is studied from the various points of view, and detailed records made of all findings.

(4) The education of nurses and internes in the actual care of cancer cases, and the contribution to the general campaign of education by the dissemination of literature, by clinical lectures, and by operative clinics. (See Section XIV.)

The combination, in the hospital, of the dermatological with the cancer departments is an important feature of the institution. An opportunity is thus afforded for the comparative study of cases, particularly those in which skin lesions are mistaken for cancer, and *vice versa.*

With the clinical facilities of the hospital, and an increasingly efficient research department, the New York Skin and Cancer Hospital may be said to occupy the position of a cancer "clearing house" for this country.

As in the case of the New York Skin and Cancer Hospital, no doubt many other special and general hospitals have devoted great attention to utilizing their opportunities for clinical investigation. Thus there has developed a sharp contrast between purely clinical investigations and those which are purely experimental, or attempts at a compromise by combining the two. The question naturally arises which of the three courses is the most advisable, and in considering the answer it is well to emphasize that there is no mutual exclusion of clinical and experimental work. The one is the complement of the other, and the question resolves itself simply into a consideration of the circumstances under which they may be best conducted, separately or combined. This, it may be pointed out, is quite a different proposition from the question considered later, of whether or not it is advisable to urge increased hospital provision for cancer patients.

THE POSSIBILITIES OF CLINICAL AND EXPERIMENTAL WORK AND THE UTILITY OF COMBINING OR SEPARATING THEM

The present point of view with reference to the possibilities of clinical and experimental work and the utility of combining or separating them, may be reviewed as follows:

1. There are hospitals where only clinical or surgical investigations can be made, *i. e.,* each operation can be regarded in the light it sheds in advancing knowledge of the disease or of surgery. There can be no doubt that in the past surgery has enormously advanced knowledge of the mode of origin, progress, and nature of cancer, but, as with purely microscopical (histological) investigations, progress is now stayed. Such hospitals can assist investigation by efforts at elucidating the problems of metabolism and biochemistry, which conceivably lie at the foundation of much of the mystery of cancer. They will finally determine when a reliable treatment has been found.

2. There are hospitals where clinical and surgical work is combined with pathology, but experiments on animals are barred. This has no advantage over institutions of the first class, except that "living pathology," as it has been described, is combined with morbid anatomy, and accurate statistics of the causes of death are obtainable, which it is hoped will some day demonstrate, in many cases, that the disease had been removed and that death was not from cancer.

3. Hospitals of the first and second types, in which experiments are permitted. In such hospitals, unless the finances are specifically assigned to patients and to animals, experimentation is handicapped by want of funds, because humanity and sentiment are always making claims for provision for patients or for additional beds for more patients.

4. The investigation of cancer may be entirely separated from the obligation to treat it. Thus money may be devoted

entirely to investigation without humanitarian scruples. This form of research has been developed to the highest pitch in the case of the Imperial Cancer Research Fund, which has no specific connection with any particular hospital. The arrangement does not imply that the workers are barred from access to clinical material; on the contrary, they have had in the past equal access to all the hospitals in London, and to as many in the provinces as was practicable, in connection with clinical and pathological statistics bearing upon diagnosis. In the future, should occasion arise, the same connections could be established again, and certainly would be were a scientifically verified cure discovered.

The purely scientific arguments against increasing hospital accommodation, on the plea that it would give increased facilities for research, have been set forth by Bashford,[1] who, it will be noted, pays a tribute to the important rôle which hospital investigation has played in the past.

"Before 1900," he says, "the mere desire to take by assault the impregnable fortress within which the mysteries of cancer were concealed, had been the incentive to an enormous expenditure of human energy. To-day, reflection on the nature of these efforts reveals how ill-advised many of them were; but, apart from the marvelous developments of surgery, there are two other notable exceptions, viz.: (1) the efforts to provide comfortable housing and adequate medical care for those beyond surgical relief from cancer; and (2) the effort to demonstrate the direct descent of the cancer from what had been previously well-behaved, normal tissues of the individual afflicted.

"The proper housing and the medical care of hopeless cases of cancer—which must not be confounded with the equipment necessary for surgical treatment, or for investigation—remains as laudable a form of philanthropic effort to-day as it was when the pioneer charity of the kind was established at the Middlesex Hospital in 1792. But it is justifiable for sentimental reasons only, and also only if it be borne in mind that it is as impracticable as it would be improvident in the highest degree, to attempt to provide such accommodation for each of the 25,000 persons who die annually from cancer in England and Wales. If the money so expended in the past had been devoted to research work purely, it would have relieved or cured the sufferings of millions, where it has merely smoothed the way

[1] Bashford, E. F.—"The Obligations Imposed on the General Practitioner by the Development of the Experimental Investigation of Cancer," *The Practitioner*, November, 1911, p. 337.

to the death of hundreds; for, in the present state of knowledge, this is all that such provisions can do, and it has been a proper restriction of its activity in the past. This statement is not made for lack of sympathy with the sufferings of the 25,000 who, denied the privileges of the one or two hundred housed in cancer asylums, die in poorhouse infirmaries, or at home surrounded by relatives, needlessly afraid of what may be the consequences of their daily intimate association with the afflicted; but is made because of the conviction that some portion of the imperfect, but improved, knowledge made available for treatment only in recent years might have been made applicable long ago.

"The enormous improvements in the surgical treatment of cancer are, with the single exception of Lister's unique services, the result, not of the revolutionary conceptions of genius, but of the labour of those who had no opportunity to avail themselves of experimental methods, because such methods had not entered upon a rational phase. Conclusions which experiment speedily arrived at, *i. e.,* within three years, afforded decisive proof of the validity of all that lies at the basis of the early surgical removal of the disease, although this treatment has been deduced from much more laborious and more prolonged investigations, and from observations often admitting only of ambiguous interpretation. This treatment had to contend with all possible forms of reasonable and unreasonable opposition; but it held its own, and the subsidiary part played by experiment in justifying it will be related later.

"To attempt to provide cancer asylums for all cancer patients is impracticable, because the disease is not usually recognized sufficiently early to make it of use in treatment. It is also impracticable on the score of expense, and it would be an improvident expenditure of money and energy. It is improvident mainly for two reasons. First, as will be explained later, the cancer from which any individual suffers has been demonstrated experimentally, within quite recent times, to be dangerous to the individual in which it arises, and only rarely, if at all, and even then only in special experimental conditions in the lower animals, dangerous to any other individual. With proper care as regards cleanliness, all that is offensive to those associated with a cancer patient can be avoided. The disease is neither infective nor contagious in the popular sense of the words, and the actual presence at the present moment in England and Wales of some 50,000 persons suffering from cancer, constitutes no danger to those with whom they are brought in contact, and no national peril; still less is it a national obligation to separate them from the enjoyment of surroundings they perhaps love the more because of the knowledge that it will not be for long.

"Secondly, it has become demonstrably improvident to provide cancer asylums for inoperable cases, because of the little that can be done, once the resources of surgery have failed or been refused, and of the certainty of a lethal end; but more particularly it would be improvident to-day, as a means of helping future sufferers, because the limitations imposed by studying the disease solely in the human subject brought the advance of knowledge to a standstill. Without new guidance all has been learned that can be learned from the study of the final stages of its clinical course, and by post-mortem, microscopical, bacteriological, and chemical examinations. But even if this standstill in the advance of knowledge had not been the real cause for the widespread public alarm at the end of the nineteenth century, how could adequate, or even any, financial assistance whatsoever be devoted justifiably to research work in any hospital, whether receiving cases still within surgical aid, or specially devoted to the reception of cancer patients hopelessly incurable, unless the money so employed was specially ear-marked for this specific purpose? The number of patients requiring relief would exhaust the greatest financial resources. The utter hopelessness of the practitioner in dealing with inoperable cases of cancer is the principal vindication of the need for resort to experiment on animals.

"Whilst the investigation of cancer must have as its ultimate goal the successful treatment or prevention of the disease, it by no means follows that this goal will be attained by directly going for it, and the treatment of cancer must, because of our ignorance, be sharply distinguished from its investigation. From the standpoint of what is practicable and politic, treatment and experimental investigation are also wisely maintained apart. Especially is this the case when the exigencies of investigation necessitate resort to indirect methods, *e. g.*, to experiments on animals, or, in other words, to a frank confession of helplessness when restricted to the study of cancer in man. This segregation is also important where the association of treatment with investigation is apt to oblige the investigator to depart from the only true path to follow in the pursuit of knowledge, and to compel him to search directly for results surmised to be capable of immediate application to the treatment of the human subject. At the beginning of 1900, with the exception of one or two very small foundations, no money whatsoever was available, either at home or abroad, for the specified object of encouraging any kind of investigation of cancer, and the medical profession, as a whole, were ignorant of the fact, or actually denied. that cancer occurred in animals."

SUMMARY

The manner in which scientific inquiry is conducted, and the results speedily spread broadcast throughout the world, demonstrate how each center of investigation is being influenced by what goes on in all the others. It is also easily evident that at any one important center a special line of investigation will be better carried out than at all the others; indeed, the special investigations with which the important centers have come to have their names associated fully demonstrates this point. Clearly recognizing this, the best investigators do not permit themselves to be diverted from the paths they have struck out by the results arrived at in laboratories not their own. In the same way revolutionary discovery made clinically would react on the laboratory worker, and the latter would likewise at once influence the clinician. Hence it appears that the two are best separated at present. Where there is an abundance or superabundance of clinical material, attention should not be diverted by an inadequate experimental department, and, *vice versa,* the experimenter should not have the "bogey" of hunting directly for a cure ever before his eyes, by being brought into direct contact with the human suffering he is powerless to relieve because he is neither a surgeon nor a physician.

This is a matter quite distinct from the question of providing increased hospital accommodation for cancer patients, especially for incurable sufferers, as discussed in Section XIII. As a means of promoting the investigation of the disease, its disadvantages have been set forth above in a quotation from Bashford, but we shall again consider it from the standpoint of its being a philanthropic duty until such time as science relieves the community of this burden of suffering.

The creation of committees or funds and the provision of laboratory accommodation is in the end of little avail, as the course of events in the last ten years has shown. Except where the right workers have been secured and allowed to develop their ideas untrammeled, little or no progress has been made, and laboratories in local centers have come to an end because local support ceased to be obtainable for investigations, the slow progress of which the layman could not comprehend.

SECTION II

GENERAL DISTRIBUTION

Cancer was formerly believed to be confined to the human species, and to the higher, or so-called civilized, races. Savage and other primitive races were thought to be exempt. With the inauguration of modern cancer research, investigations have tended to convince many that malignant tumors may arise, under certain circumstances, in any multicellular animal organism. Some students of comparative pathology have gone so far as to express the opinion that an etiological similarity exists between abnormal budding in the vegetable world and tumor-formation in the animal kingdom.

Environment and nutrition have been suggested as dominant factors in the production of these pathological outgrowths alike in plants, lower animals, and human beings. It has been claimed, for example, that in many recorded instances of vegetable tumors, the trees or other plant subjects bearing them lived under adverse circumstances, as in low, damp places, where the ground was constantly watered by sewage-contaminated streams, the plants being thus improperly nourished.

It has been thought that animals living in their native surroundings, those to which their organisms have become thoroughly adapted, are presumably very little subject to tumor-formation. Transplanted to a different environment, as to a zoölogical garden, or to a domesticated existence, the liability to new growths was said to increase. This contention is difficult of proof, figures upon the subject being comparatively meager.

In like vein it is argued with reference to man. In his primeval condition, with the simple life, which differs but little from that of the lower animals, he has been thought to be very little subject to new growths, particularly to those of a malignant character. With changed environment, it is claimed by some, there comes an increase in susceptibility to cancerous diseases, this susceptibility becoming more marked as civilization develops; in other words, as environment changes.

A study of the general distribution of cancer and other tumor formations is interesting and not without profit. So long as the essential cause of malignant neoplasms remains unknown, it may be hoped that investigation of the occurrence of such neoplasms will aid in giving direction to the search for etiological or causative factors.

The steady increase in the number of deaths recorded from cancer among intelligent and well-to-do members of society is calling forth added interest in the so-called "direct method" of studying the disease. This method involves investigation of the ethnological and geographical distribution of cancer, a close insight into questions of racial predisposition, social conditions, habits of life, diet, climate, soil, and the various other factors which from time to time have been proposed as contributory causes in the production of malignant new growths.

No disease, with the possible exception of tuberculosis, has called forth more study from the statistical point of view than has cancer. From all parts of the world figures and other data have been compiled concerning the incidence of the disease, and more and more each year attention is being directed to the ethnological and geographical conditions which may have some possible connection with its occurrence.

It is proposed in this section to discuss the ethnological and geographical distribution of cancer in man, to give some of the more recent statistical and other data collected by various authorities concerning the occurrence of malignant and non-malignant neoplasms in lower animals, and to review briefly some of the findings concerning cancer-like formations in plants. The enormous mass of material of this character which has been published will be drawn upon for such facts or theories as seem to throw most light upon the etiology of the disease, and for those most significant as regards prophylaxis, diagnosis, and treatment.

At the present stage of development of the cancer problem, it is impossible to reach definite conclusions from such information, although inferences may be drawn, subject, of course, to modification as further knowledge is obtained.

Study of the question from this point of view, more and more clearly demonstrates the practically world-wide distribution of cancer. At the same time it should emphasize the fact that there is undoubtedly a variation in the frequency with which cancer is recorded among different races, in different countries, and in different localities of a given country. Comparative investigations also tend to convince the careful student of statistical records that poverty, filth, and squalor, the great producers of infective diseases, are not the necessary concomitants of cancer. Such investigation seems, however, to emphasize the view that simplicity of life lessens the danger of the disease.

The bearing that a study of the ethnological and geographical distribution of cancer may have in directing experimental work and in clearing up certain ideas concerning the pathology of the disease, will be discussed in other sections.

CHAPTER I

BOTANICAL DISTRIBUTION

It is believed by many students of comparative pathology that tumors analogous to malignant and non-malignant neoplasms in man and animals may be found in vegetable organisms. Noël[1] has gone so far as to hold that certain "arboreal cancers" may be communicated to human beings and animals by contagion.

A distinction is made by students of plant pathology between the tumor formations which result from abnormal bud evolution, and which are alleged to be analogous to cancers in man and animals, and the tumor-like gall formations which are due to the action of parasitic or other extrinsic irritants. Those who still hold to the parasitic theory of the origin of cancer would naturally not make this distinction.

It is held by some that cancer and cancer-like growths, whether of plants, animals, or man, are due to changes in nutrition which cause altered growth and impaired development, the fundamental physiological and pathological processes being the same in plants and animals. Others have assumed that some of the tumor formations (galls) of plants are proof of the parasitic origin of cancer in man and animals.

Notable among the last-named vegetable "cancers" are the tumors of the cauliflower and other members of the cabbage family, known in the German as "Kohlhernie," and in English as "club-root," and "finger-and-toe disease." This disease is due to a protozoan, the *Plasmodiophora brassicæ*,[2] and is thought by some upholders of the parasitic etiology of carcinoma to be analogous to the proliferation of epithelial cells in

[1] Noël, L.—"Sur la topographie et la contagion du cancer." *Rev. des mal. Cancereuses*, Paris, 1896-1897, II, pp. 137 and 201; also: Thèse de Paris, 1897.

[2] "Finger-and-toe disease," "club-root," "hanbury," "Kropf," "Kohlhernie," as the disease is variously called, attacks all kinds of cabbage, kale, kohlrabi, and other edible cruciferæ. The disease was first recorded in Scotland, in 1789. It is now distributed in all places where cabbage, turnips, and allied vegetables grow on a large scale. The malformations which characterize the condition are the result of hypertrophy of the host-cells due to a stimulus exerted by the *Plasmodiophora brassicæ.*

that disease. The analogy is carried further; the "cancer bodies" described in human malignant tumors are supposed to be protozoa, and these unicellular organisms are considered to be the cause of cancer.[1]

It has been claimed by some investigators that these protozoa, in spore form, are found in the cells of the diseased plants. After experimentation, some authors have stated that these organisms, inoculated into rats and guinea-pigs, produce nodules resembling, in some cases, large-celled sarcoma, endothelioma, or granuloma, but not producing epithelial proliferation. Von Tubeuf,[2] on the other hand, considers that plant "cancers" cannot be compared with cancers in man. Animal and vegetable parasites or frost may cause tumor-formations in plants. His experiments with the inoculation of animals with *Plasmodiophora brassicæ* produced nothing analogous to cancer.

Another illustration of irritative cell proliferation in plants is seen in tumors due to abnormal bud evolution, resulting from fungus or parasitic irritation, of which the "witches' broom" is an example.

The point of infection by the *extrinsic* irritative element is the starting place of the "witches' broom." The "broom" generally originates from a bud which has been infected during the previous summer. This bud presumably produces a twig capable of abnormally increased growth. The original leader shoot, of which some lateral shoot develops into a "witches' broom," shrivels and dies, the hypertrophied branches seeming to absorb its contents.

William G. Smith, Lecturer on Plant Pathology, University of Edinburgh, has found asci (small membranous bags, in which the spores of lichens, fungi, etc., are inclosed) of a fungus on the leaves of the "witches' broom" so commonly seen on the birch trees of Scotland. Mites are also supposed by some to cause these abnormal bud formations.

Erwin F. Smith,[3] of the Bureau of Plant Industry, United States Department of Agriculture, has maintained for several years that the crown gall of plants resembles malignant human tumors, and that study of the former may be made to throw

[1] Nichols.—"Third Report of Harvard Cancer Commission," 1905, p. 79.

[2] Von Tubeuf.—"Ueber Krebs bei Pflanzen," *Verhandl. des Komites für Krebsforschung*, Heft 1, p. 74, Berlin, 1902; also: *Deut. med. Woch.*, 1902, Vereins-beilage p. 96. See also: von Tubeuf and Smith—"Diseases of Plants Induced by Cryptogamic Parasites," 1897, p. 524.

[3] "The Structure and Development of Crown Gall: A Plant Cancer." U. S. Department of Agriculture, Bureau of Plant Industry, Bulletin No. 255, June 29, 1912.

light upon the pathology of the latter. With the discovery of a tumor strand and of a stem structure in secondary tumors in leaves, this view received added interest. He believes that the crown gall possesses peculiarities of neoplastic growth which remove it from all ordinary plant diseases and which place it in the category of the true tumors (atypical blastomas). In other words, he contends that "crown galls are to all intents and purposes cancers." These tumor-formations in plants have been found to be due to a schizomycete, *Bacterium tumerfaciens,* Smith and Townsend. The bacteria are said to be located inside the cells. The stimulus of the presence of these organisms causes the cell to divide by abnormally throwing it out of balance, this stimulus probably extending to many surrounding uninfected cells.

Among other statements in his résumé of the studies made by himself and his coworkers concerning the crown gall Smith says:

"Crown galls occur on a great variety of plants, but not always on the crown; any part of the root or shoot is liable to attack."

"They are all of parasitic origin, unless the one on the beet studied by Jensen, Reinelt, and Spisar, in Europe, should prove an exception."

"We have isolated the parasite from 24 species belonging to 14 families of phanerogams. Some species have resisted infection."

"The infectious nature of the organism isolated has been proved by hundreds of inoculations and its ability to produce galls on other plants than the one from which it was isolated by many cross inoculations."

"The parasite has been shown to occur not only in the primary tumor, but also in the secondary tumors and in the connecting tumor strand."

"The tumor sends out roots (tumor strands) into the normal tissues. These may extend for some distance from the tumor—how far is not known."

"In the substance of these deep-lying strands secondary tumors develop. These gradually rupture their way to the surface."

"The secondary tumors tend to take on the structure of the primary tumor, e. g., if the latter is in the stem and the former in a leaf, the secondary tumor shows a stem structure."

"The development of this disease is regarded as closely paralleling what takes place in cancers of men and animals."

"There are no true metastases in crown gall, but this does not, to our mind, militate against the comparison, for whether a cancer shall be propagated by floating islands of tissue, or only by tumor-strands, appears to be a secondary matter depending on the character of the host tissues rather than on the nature of the disease. The essential element is the internal stimulus to cell division."

It goes without saying that investigators who have not subscribed to the parasitic origin of cancer fail to recognize the analogy which to Smith and his coworkers seems so patent. Notably the presence of the parasites in Smith's secondary growths is in contradiction to the way in which secondary growths arise in man. Moreover, Jensen [1] has described tumors of the beet which he was able to transplant so that a tumor of a red beet grew in a white beet, and *vice versa;* but Jensen could not find any parasitic cause for these growths.

The olive is particularly subject to tumors known as "olive knots," which vary from the size of a pea to that of a hazelnut. These tumors are due to the action of bacteria. The twig on which the knot or gall forms, dies above the gall. The willow, birch, pine, and other trees are subject to a similar disease. Certain pines, particularly in the region of the Alps, are especially subject to these twig-galls, which are larger than those of the olive.

Vegetable tumors, particularly those known as galls, are regarded by some students of plant pathology as being the result of an excessive local cell proliferation initiated by the irritative action of a virus of insects which make wounds for the purpose of depositing in them their ova. Others hold that these galls result from the activity of the larva after it has been hatched, and not from the sting of the adult insect.

It is interesting to note that until about two hundred years ago galls were supposed to be of purely vegetable origin, and the insects in them were thought to have been produced by spontaneous generation. Malpighi, in the second half of the seventeenth century, was the first to show the insect origin of galls.

Calkins,[2] discussing the suggested analogy between vegetable and animal and human tumors, says: "The advocates of the parasite theory believe that the cancer cell became a parasite in the above sense [that the cancer cell is a parasite itself], not from any derangement of metabolic processes, nor from any vague, hypothetical, inherent tendency to cellular anarchy, but because of susceptibility to the poisonous stimulus

[1] Jensen, C. O.—"Von Echten Geschwülsten bei Pflanzen." Travaux de la 2 Conference Internationale pour l'Étude du Cancer, 1910, Paris, 1911, p. 243.

[2] Calkins.—"Protozoölogy," p. 209.

of some parasite. In this they are supported by the facts of gall formation in plants, where a known poison, secreted by insects, stimulates the latent division energy of the plant cells, and a tumor is produced. The counter argument, so often made, that such abnormal growths are nothing like cancer, is certainly true; the analogy, however, is not with the form which the growth assumes, but with the cell which is stimulated to divide by the activity of a parasite. Among other things, the gall differs from the cancer cell in having no infectivity, the stimulus not being continuous.

"Another analogy is drawn from the great tumor-like growths in certain vegetables (cruciferæ), due to the presence in the root cells of a protozoön parasite, *Plasmodiophora brassicæ*. These growths, known as club-root, hanburies, fingers-and-toes, etc., are highly infectious, and are frequently a serious menace to market gardens. The organism causing the tumors penetrates the root hairs of the cabbage or other allied vegetables in the form of a minute ameboid flagellate (Woronin, 1878, Prowazek, 1905). Two or more may enter the same cell, where, immersed in the fluid cytoplasm, they lose their flagella and grow into larger ameboid organisms. Later, these ameboid cells fuse, forming, as in all myxomycetes, a syncytium or plasmodium. The infected cells are caused to divide by the presence of the parasite, the infected cells thus carrying the disease-causing germ, which in itself apparently has no power of migrating from cell to cell (Prowazek, 1905). After a number of such divisions the infected cells undergo hyperplasia or hypertrophy; the pressure and possibly the toxins from the organisms cause neighboring cells to proliferate until large abnormal growths result."

Bland-Sutton,[1] discussing Cohnheim's theory, expresses the belief that "tumor germs" actually exist in the body. "The erratic growth of such undeveloped portions of tissue may well be illustrated in a simple way by examples from the vegetable kingdom. The stems of trees and woody plants form a large number of buds, most of which grow into branches. Some of these remain undeveloped for a time, and then, instead of forming a normal branch, they grow erratically, and form a swelling or woody tumour of irregular shape, which may attain a large size. Such a tumour of a tree is termed a xyloma. The bud-like character of such woody tumours is shown in an interesting series presented to the museum of the Royal College of Surgeons by Mr. Stephen Paget. From some of the tumours buds have grown into a minute branch. Every swelling on a tree,

[1] Bland-Sutton.—"Evolution and Disease," London, 1890, p. 241.

however, is not a woody tumour or xyloma; many are due to insect bites."

In addition to the vegetable tumors which arise in consequence of the action of extrinsic irritants, other manifestations of abnormal bud evolution are said to result from intrinsic causes, such as changed or abnormal nutrition.

Williams[1] classifies these tumor-formations, which are sometimes placed in the category of "malformations," under the following groups:

1. Circumscribed woody nodules commonly found beneath the bark of the beech, elm, oak, cedar, holly, and other trees. "Knauer" is a term commonly applied to these formations.

2. Continuous tumors, comparable with the exostoses of human pathology, and appearing as woody outgrowths of the trunk or branch.

3. Burrs, "broussins," the free and continuous formation of proliferous buds, shoots, and stunted branches.

Penhallow, Macdonald Professor of Botany, McGill University, has reported an interesting instance of continuous tumor-formation. The tumor was twenty feet long, and hung free, being attached at the upper end only. There was nothing to indicate intermittent, longitudinal growth, there being an entire absence of rings or scars to mark successive periods of development, such as were found in the leaf scars and nodes upon young branches of the same tree. From this it was inferred that the entire growth took place within one season. The tumor-formation was not an aerial root, such as is found in tropical latitudes. Penhallow concludes that the outgrowth had its origin in a lesion of the bark, the precise nature of which could not be determined. Some investigators would attribute this to an extrinsic irritative stimulus, whereas others would consider it due to an intrinsic cause, as changed or abnormal nutrition. The same might be said of the other classes of tumors cited by Williams.

SUMMARY

The suggested analogy between the various so-called tumor-formations in the vegetable kingdom and benign or malignant neoplasms in the animal kingdom has not been established by the evidence offered. The statement that "crown galls are to all intents and purposes cancers," is apt to be misleading, since it presupposes the parasitic origin of cancer—a supposition not established by indisputable evidence.

[1] Williams.—"The Natural History of Cancer," 1908, p. 120 *et seq.*

Biologists as a whole are very unwilling to draw close comparisons between the higher plants and the higher animals. The continuous growth, which is characteristic of many plants that have long been propagated by cuttings, is illustrated in the Lombardy poplars, spread all over Europe in the time of Napoleon. These trees have in many instances reached the end of life, but, by making fresh cuttings, new trees are again grown. So that there seems to be no end to some individual plant organisms, as contrasted with the definite end set to the life of all higher animals. In this respect the propagation of cancer by implantation or grafting on other animals must be sharply distinguished from the grafting of plants, since the former remains a single tissue, whereas it is the rule for vegetable grafts to reproduce the features of the entire organism. to produce flowers and seed.

CHAPTER II

ZOÖLOGICAL DISTRIBUTION

DESPITE the many difficulties involved in the study of the zoölogical distribution of cancer, much interesting material has been collected, and certain lines of inquiry have been very definitely indicated. Particularly does this apply, in the latter regard, to certain of the mammalia commonly classed as domesticated animals, as, for instance, horses, cows, sheep, dogs, cats, pigs; and also to certain others not usually so considered, yet which have so intimate a connection with domestic life as to come within its category, such as tame rats, mice, rabbits, and guinea-pigs.

The study of the zoölogical distribution of cancer has established beyond further question the fact that malignant new growths are not, as was formerly held, a purely human affection. It has shown, as Sir John MacFadyean maintained—a view which Bashford and Murray have confirmed—that all the histological types of malignant new growths in man are recognized in domestic and wild animals.

Other questions which have been elucidated by the study of cancer in animals, and which will doubtless be further clarified as these investigations progress, are:

1. Influence of environmental changes, including diet.
2. Influence of chemical and other irritants.
3. Influence of heredity.
4. Age incidence.
5. The influence of use on organs—site incidence.

Influence of Environmental Changes, Including Diet.—Naturally enough, domesticated animals and wild animals living in captivity have furnished the majority of known examples of cancer in the zoölogical world. Among the latter, however, the disease is comparatively rare, doubtless largely owing to the fact that so great a proportion of wild animals kept in captivity die young, and hence before the so-called "cancer age."

With regard to the frequency of cancer among wild animals living in their native habitat, there are conflicting opinions. Some students of pathology hold that among such the disease is very rare, if not entirely unknown, while others claim that it has been found with sufficient frequency to indicate that it is not uncommon.

Bashford[1] holds that the discovery of malignant new growths in wild animals depends upon the relative facilities which exist for careful examination. He cites, in this connection, two instances of malignant new growths in fish living in a state of nature, and one in a wild mouse. This contention is in line with the statement that "the great diversity of food, habit, and conditions of life generally, in animals in which cancer occurs, shows that such external agencies have no causative influence."

Other investigators by no means subscribe to such statements, but hold that every phase of the study of the occurrence of new growths in animals is a verification of the theory that cancer incidence is very largely dependent upon environmental changes or abnormalities.

Influence of Chemical and Other Irritants.—Another phase of the problem which has acquired enhanced importance in consequence of the study of the zoölogical distribution of cancer, is the effect of chemical and other irritants, not only in the production of the disease, but upon the rate of development in animals already affected. This subject has been studied particularly in fish, and especially in artificially bred fish. It is supposed that in-breeding and certain chemical properties of water induce simple goiter which, later, undergoes cancerous degeneration. Most of the mouse tumors found among those of one breeder were cancers of the breast in old females long used for breeding purposes, the breasts, presumably, being subjected to prolonged irritation in the suckling of so large a number of offspring. The influence of chronic irritation in the production of cancer is seen in the so-called "brand-cancer" of cattle, and the "horn-core" or epithelioma at the base of the horn, in Indian draught animals.

Influence of Heredity.—It has been possible to subject the question of the influence of heredity to actual experimental tests in studying laboratory animals. Bashford, and especially Murray, of the Imperial Cancer Research Fund, and Tyzzer, of the Harvard Cancer Commission, have been working along this line.

Bashford[2] says on this subject: "In surveying the incidence of cancer in the vertebrate kingdom, one has been struck

[1] Scientific Reports, Imperial Cancer Research Fund, No. 1, 1904, p. 7.
[2] "Heredity and Disease—Cancer Heredity," Proc. Roy. Soc. of Med., London, November 18, 1908, Vol. II, Part I, R. S. M., p. 63.

by the fact that certain forms of cancer appear to preponderate in different classes. It is, of course, obvious that the incidence in representatives of different zoölogical classes must differ, since, e. g., structures peculiar to mammals are absent in other vertebrates. But if we consider the mammalia themselves, it appears probable that some species are very liable to forms of cancer from which others, even nearly allied, are relatively or altogether exempt, as illustrated, e. g., by the variations in the frequency with which cancer of the uterus or mamma occurs. Cancer of the breast, so common in the human female, is also common in the mouse and dog, but practically unknown in the cow, which, however, suffers quite frequently from primary growths of the liver and adrenal. These tendencies are so constant that it is difficult to escape the conclusion that they depend on innate characters which are hereditarily transmissible, and there can be no doubt as to their ætiological importance, although we cannot penetrate to their meaning.

"Even in the same species we meet with similar idiosyncrasies, e. g., in the greater liability of the grey than of other horses to melanotic sarcoma. It may, of course, be argued that these peculiarities of incidence of the disease are determined by peculiar environment or by the use to which the organs are put in different species, although this would hardly hold for grey as contrasted with other horses, the disease in question affecting only the pigment-cells of the skin. If we compare the tame albino mouse with the wild grey mouse the incidence of cancer is parallel in them, although the two varieties live under very divergent conditions; therefore the liability of the mouse to carcinoma of the mamma appears to be due to an innate tendency.

"When we compare the large natural groups of vertebrates, or even the species of the mammalia, the grounds on which we may assume that differences in the incidence of cancer are innate and hereditarily transmitted appear safe. But when we come to compare the differences in the incidence of cancer in the individuals of a species we are not on such certain ground."

From these observations it will be seen that, while the zoölogical distribution of cancer has thrown light on the question of heredity, there is much yet to be learned in this regard. The subject will be considered more in detail in Section III.

Age Incidence.—It is generally conceded that in animals, as in man, cancer is more liable to occur in aged than in young subjects. Inasmuch as the length of the life cycle varies greatly in different species of animals which are known to be subject to cancer, it is presumed that the latent period, the period of development which precedes the manifest occurrence of cancer, likewise varies.

Bashford has pointed out that because domestic animals, with the possible exception of horses, pet dogs and cats, are not frequently allowed to attain old age, the total number reaching the most favorable age for the development of cancer is small. So, too, with wild animals, whose struggle for existence possibly permits relatively few to reach old age, a fact which might account, in part at least, for the rarity of cancer among them. "A comparative study," he says, "of the age-incidence of cancer among domestic and wild animals of varied species will certainly give comprehensive information on the relation of the incidence of cancer to the rapidity with which maturity is attained. Light may also be thrown on the reasons underlying the higher cancer-rate of late life."

Influence of Use on Organs—Site Incidence.—The site incidence of cancer seems to vary with different animals, and will be included under the discussion of the occurrence of cancer in specific classes of subjects.

DOG

Among domesticated animals, dogs seem to lead in point of frequency of occurrence of cancer. Thus Sticker [1] tabulated 1,312 cases of malignant tumors in domestic animals, 738 of which were in dogs. Of 60,471 dogs which were treated in the Berlin Thierärztlichen Hochschüle from 1886 to 1894, 2,871 had some form of tumor, 1,154 of which, according to Fröhner, were cancerous. Other investigators give even higher percentages. The dog bears out what has been said concerning age incidence. The disease occurs most frequently in old dogs, a large proportion being found in dogs from 5 to 10 years old. Malignant tumors in dogs under 2 years of age are said to be very rare.

Many of the forms of malignant new growths found in man are also to be found in dogs, as are likewise various non-malignant tumors. Carcinoma, of the malignant tumors, seems to be of the most frequent occurrence in the canine family, the mamma standing at the head of the list of the sites affected, this region being involved in 45 per cent. of cases (Sticker); the skin in 21 per cent.; anus, 21 per cent.; liver, 3 per cent.; and less frequently, kidney, testis, penis, prostate, eye, bladder, vagina, lung, thyroid, ovary, etc. (Williams, p. 95).

[1] Sticker, Anton.—"Ueber den Krebs der Thiere, etc."—*Arch. für klin. Chirurgie,* 1902, Bd. LXV, pp. 616, 1023.

The extreme rarity of gastric and uterine cancer in dogs is interesting from a biological point of view. The relatively recent development of the uterus, formed by fusion of both Müllerian tubes, produces in this organ, in the higher animals as well as in man, a condition of great instability and hence one highly susceptible to tumor-formations.[1]

The relative rarity of mammary and uterine cancer in dogs, as compared with man, is explained by Woods Hutchinson as due to the fact that dogs, unlike human beings, seldom live beyond the period of reproductivity.[2]

The extreme rarity of cancer of the stomach in this animal is explainable upon the basis of the relative stability of organs which, from an evolutionary point of view, are of earliest development.

CAT

The records of the Veterinary Pathological Institute of Berlin show that of 34 cats examined, from 2 to 5.9 per cent. were affected, and various individual cases of cancer in cats are reported by different observers. The mammary gland and the skin are apparently most liable to the disease, although various other parts are known to be attacked.

Spencer[3] reported a case of carcinoma involving all the mammary glands of a cat.

Field[4] reported a scirrhus of the mammary gland of an old cat, and a mammary cancer with metastases in lymphatic glands, lungs, heart, stomach, intestines, uterus, ovaries, kidneys, and suprarenal capsules. Malignant new growths of various types have been reported in different localities in the cat.

HORSES

Horses, mules, and asses are subject to malignant new growths. Of 215,037 horses examined at the "Hochschule" Veterinary Clinic in Berlin, according to Sticker, only 103 were victims of malignant tumors. This is only 0.046 per cent., which is somewhat at variance with the reports of veterinary journals and other observers (Williams, p. 99).

In horses the parts most frequently affected by primary cancer are the antrum and adjacent naso-oral cavities (16 per cent.), and the penis (16 per cent.), the kidney, skin, lungs,

[1] Hutchinson, Woods.—"Studies in Human and Comparative Pathology," 1901, p. 257.

[2] *Op. cit.*, p. 263.

[3] Spencer, W. G.—Trans. Path. Soc., London, Vol. XII, 1890, p. 400.

[4] Field, Eva H.—"A Contribution to the Study of Malignant Growths in the Lower Animals."—*Jour. Am. Med. Assn.*, 1894, Vol. XXIII, p. 982.

and pleura, and various other parts being affected with relatively less frequency. With the horse, as with other animals, those that have been castrated seem more prone to the development of malignant neoplasms.

BOVINES

In the bovines, cancer is common in the liver, stomach, and adrenal, according to the figures of the Imperial Cancer Research Fund. Leo Loeb [1] has stated that carcinoma of the caruncula of the eye is common in a certain district of the United States. The rarity of cancer of the udder (mamma) of the cow is very striking in view of the frequency of inflammatory processes in that organ and the extent to which its function is abused.

The influence of chronic irritation in the production of cancer, known as "brand-cancer" and "horn-core" (epithelioma at the base of the horn), as seen in draught animals in India, has already been mentioned.

SWINE, SHEEP, AND GOATS

Swine, sheep, and goats are very rarely reported as affected with malignant neoplasms, probably because, as a rule, they are slaughtered young, before the cancer-age begins.

In swine, the kidney, liver, and skin are the sites involved in the major proportion of reported cases, although various other regions may be affected.

In sheep, the liver seems to be a chief seat of primary involvement. Among other sites mentioned as being affected are the maxillary bone, the eye, the orbit, and the lung.

In goats, cancer is more rarely found, judging from recorded cases, than in any other domesticated animal. This, however, may be explained because of the relatively small number of goats in existence.

WILD ANIMALS IN THEIR NATIVE STATE AND IN CAPTIVITY

Tumors have been found in the following wild animals: lion, tiger, leopard, bear, rhinoceros, hippopotamus, porpoise, camel, opossum and other marsupials, beaver, whale, marmot,

[1] Loeb, Leo, and Johnson, George.—"On Carcinoma in Cattle," *Medicine,* April, 1900, p. 286.

Also: Loeb.—"Ueber den Krebs der Thiere," *Arch. für klin. Chir.,* 1903, Bd. LXX, p. 845; "Ueber das endemische Vorkommen des Krebses bein Tier," *Centrlbl. f. Bakter.,* Bd. 37, 1904.

kangaroo, monkey, wild raccoon-dog, deer, rabbit, mouse, rat, and guinea-pig.

Harlow Brooks,[1] Pathologist of the New York Zoölogical Park, says concerning the occurrence of neoplasms in wild animals: "True neoplasms in wild animals which live under conditions closely approximating the natural are extremely rare. This is true of relatively pure and uncontaminated species."

In the 2,647 mammals under care for the five years preceding this communication (1907), but a single case of true neoplasm occurred. Of these animals, 744 came to complete autopsy without a single new growth being found, with the exception of the case cited by Brooks, which is detailed below. This rarity of tumors under these circumstances may be accounted for, in part at least, by the fact that such animals do not live to an advanced age (for the given species).

In addition to these, Brooks reports having studied a considerable series of animals secured and dissected in the field by himself or other physicians. Not a single case of neoplasm was found among these animals, which were chiefly North American wild ruminants.

The case reported was that of a white raccoon-dog, which had been an inmate of the park for over two years before it sickened and died. It was captured in northern Japan and was described by Director Hornaday, of the New York Zoölogical Park, as a new species, *Nyctereutes albus*.

At autopsy the animal was found to be generally emaciated, all the viscera showed the effects of malnutrition and anemia, consequent upon the neoplastic disease. The lower two-thirds of the pelvic and abdominal cavity was occupied by a large retroperitoneal mass to which the coils of intestines were adherent. The tumor apparently originated from the left ovary, and was diagnosed as myxosarcoma.

"Great interest," quoting from Brooks, "lies in the discovery of this neoplasm in this particular animal, not only on account of the great rarity of the tumor, but chiefly because it occurred as the only example of tumor formation, in an animal of questionable purity of species. Many zoölogists do not agree that the white raccoon-dog is a pure species, but consider it a 'sport' albino, or the result of mixed parentage."

"The bearing of these observations on the general question of the etiology of tumors would seem to tend to substantiate," he

[1] Brooks, Harlow.—"Concerning the Occurrence of Neoplasms in Wild Animals, with the Report of a Case of Sarcoma of the Ovary in *Nyctereutes Albus*," *Am. Jour. of Med. Sci.*, May, 1907, Vol. CXXXIII, p. 769.

continues, "those theories attributing neoplastic formations to perversions of cell growth, a tendency well recognized to be more frequent in animals or people of imperfect development or of mixed races, or such as live under more or less artificial environment."[1]

BIRDS *

(Domesticated Fowl)

The common barnyard fowl is said to be the frequent subject of neoplasms, benign and malignant.

Instances of tumor-formation in the hen and cock have been reported by Bland-Sutton, Ehrenreich and Michaelis, Crisp, Birchmore, Patterson, Pick, and others. Peyton Rous, of the Rockefeller Institute, has lately drawn attention to the great frequency in fowls of certain connective tissue tumors, which he calls sarcomata.

The goose, also, is prone to such growths, a number of instances being on record. One of the most interesting is that of a "fibroid" tumor "as big as a large lemon," which occupied the abdominal cavity of a goose, supposedly arising from the oviduct or intestine. This specimen may be seen in the Museum of the Irish College of Surgeons (D.f. 56).

Harrison [2] reported a fibroid tumor, weighing one pound, in an old goose which died in the Clifton Zoo.

It should be borne in mind that tubercle causes the formation of large tumor masses in birds, and that the imperfect descriptions published of many of these "fibroid" tumors prevent their being accepted without reservation.

WILD BIRDS

Pick and Poll [3] have stated that malignant tumors in birds are of very rare occurrence, yet a sufficient number have been reported to show that wild birds, including birds of prey, come within the category of susceptibility to this class of disease.

REPTILES AND AMPHIBIANS

The salamander, tortoise, lizard, chameleon, frog, python, and boaconstrictor, are some of the members of these orders in which malignant and benign tumors have been noted.

[1] Third Scientific Report, Imperial Cancer Research Fund, 1908, pp. 45-47; Fifth Report, Harvard Cancer Commission, p. 133.

[2] Harrison, A. G.—"A Study in the Gardens of the Clifton Zoölogical Society," *Bristol Medico-Chirurgical Journal*, 1894, Vol. XII, p. 285.

[3] Pick, L., and Poll, H.—"Ueber einige bemerkenswerte Tumorbildungen aus der Tierpathologie, etc.," *Berl. klin. Woch.*, 1903, Vol. 40, pp. 518-572.

Murray[1] states that "Up to the present no malignant new growth has been recorded in reptiles." Bland-Sutton,[2] however, reports a case of medullary cancer in a python which had lived in the Zoölogical Society's garden for fifteen years. A fibroma in the stomach of a python was described by Pettit.[3] Koch[4] reported a papilloma of the occipital region in a lizard.

According to Murray (*loc. cit.*), new growths from amphibia are very limited in number. "They have, however, a particular interest from the zoölogical position of this group, and the clearness of the histological picture, due to the large size of the cells of these animals which have remained the classical objects of cytological study, especially with regard to cell-division, ever since Flemming published his epoch-making studies on indirect (mitotic) cell-division in *Salamandra* in 1882."

Tumors in frogs have been described by Eberth, Pettit, Pick, Smallwood, Plehn, and others.

FISH[5]

It has been suggested by Williams, and corroborated by others, that fish are particularly liable to infections of different kinds, and that many of the tumors caused by sporozoa, mycoses, bacteria, etc., etc., may be mistaken for malignant tumors.

It has been well established, however, that tumors of undoubtedly malignant character occur in large percentages among artificially bred fish. Gilruth, for example, showed that thyroid cancer in artificially bred salmon trout carried off in one year seven per cent. of the fish in the Auckland Society Hatchery, while Bonnet reported three thousand cases in one hatchery in four months. Others have reported "cancer epidemics" among artificially bred trout.

While it has been clearly shown that fish kept under artificial conditions are susceptible to cancer, it has also been shown that fish living under natural conditions are not free from this disease.

Murray, Plehn, Pick, Jaboulay, and others have contributed to the investigations concerning cancer in artificially bred fish.

[1] Murray, J. A.—"The Zoölogical Distribution of Cancer," Third Scientific Report, Imperial Cancer Research Fund, 1908, p. 47.

[2] Bland-Sutton.—"Tumors in Animals," *Jour. of Anat. and Physiology* (British), Vol. XIX, 1884-5, p. 464.

[3] Pettit, A., and Vaillant, L.—"Lésions stomacales chez un Phython de Sebo," Bull. Mus. Hist. Naturelle, Paris, 1902, p. 301.

[4] Koch, M.—Verhanndl. d. deut. Gesselsch. f. Pathol., 1904, p. 136.

[5] See General Bibliography.

Gaylord and Clowes, likewise, of the New York State Institute for the Study of Malignant Disease, have devoted considerable attention to this subject.

In connection with the work of the last-named institution, it is interesting to note the "disquieting information" given out by the United States Fish Commission, after its coöperation with the New York State Cancer Laboratory in the investigation of thyroid cancer in domesticated fish. The following statement is contained in this report: "It has been determined that a type of cancerous affection is of widespread distribution among domesticated trout and their offspring planted in the streams. Whether this disease has a causal relation to cancer in human beings, or whether the two are to be traced to even the same source, is a matter of doubt, but the annually increasing mortality from cancer in man and certain remarkable coincidences in the geographical distribution of the disease in man and fish render it imperative that it should be made the subject of minute inquiry. The matter, therefore, has not only economic but humanitarian aspects, and the consideration of the serious character of the latter prompted the President to submit to Congress on April 9, 1910, a special message advocating an appropriation of $50,000 for the construction and equipment of a laboratory adequate to enable the Bureau to discharge its plain obligations." (This appropriation was not made.)

So profound an impression did this "disquieting information" prove, that the editor of the *Fishing Gazette,* of London, in its issue for March 11, 1911, issued a "warning" concerning cancer in trout in America. "It is clearly the duty," he said, "of all who import eggs from American fish hatcheries to observe the greatest caution; in fact, to urge their Governments to prohibit the importation of such eggs."

Naturally, such a warning from the editor of *The Fishing Gazette* had its effect; in fact, so great was this effect that it bade fair to paralyze the fishing industry of Great Britain, causing such alarm among people in general that fish as an article of diet was fast falling into disuse. At this juncture of affairs, the editor of the *Gazette* appealed to Dr. Bashford, whose reply was published in the issue for April 8, 1911. Among other things Dr. Bashford said: "There is absolutely no danger of the communication of the disease from fish to man, even if the fish were not cooked, nor do I think any risk is implied by importing the eggs of the *American Salmonidæ.*"

This quieted the fears of all concerned, the fishing industry resumed its usual proportions, and the public returned to the consumption of fish without the dread of cancer.

Bashford,[1] who has had a very extensive experience with these so-called cancers of the thyroid gland in trout, had his attention again directed to this subject by Gilruth, as the result of advertisements which he inserted in the *Veterinary Record* in 1903. Since then he has again and again pointed out that these enlargements of the thyroid in trout are not to be regarded as epidemics of cancer in fish. He admits, however, that cancer may develop occasionally on goiter. The continued reiteration of exaggerated statements regarding this goitrous disease, and its presentation to the public as if it were evidence of the epidemic occurrence of cancer and of the infective nature of malignant new growths, are greatly to be deprecated.

Bashford and Murray[2] stated in 1905: "We have examined sixteen cases of undoubted malignant new growth in fish alone, whereas no authentic case was known at the outset of these investigations. . . . 1,500 growths in fish have been reported to us. The specimens examined have included fish infested with Nematodes and Cestodes, bacterial and mycotic infections, malformations, benign tumours, and infective conditions of undetermined ætiology. In trout, tumours of the branchial region are frequent and often difficult to distinguish from true malignant new growths because the thyroid tissue extends diffusely along the branchial arches and a general hypertrophy closely simulates a primary growth with secondary nodules."

In addition to Gaylord, another American investigator, David Marine, has done very careful work, the result of which is to entirely justify the attitude which Bashford has assumed. In his most recent paper[3] he summarizes his previous experience as follows:

"Investigations (1) made at the trout hatchery of the Blooming Grove Hunting and Fishing Club during 1909 and 1910, showed that all the fish were then goitrous. It was found that the thyroid hyperplasia began in the fry as soon as feeding was instituted, and advanced overgrowth was present at the fourth month of extra-oval life; that the overgrowth progressively increased to the stage of clinical detectability, as ascertained by the reddening of the pharyngeal floor over the thyroid area,

[1] First Scientific Report, Imperial Cancer Research Fund, 1904.

[2] "The Statistical Investigation of Cancer," Second Scientific Report, Imperial Cancer Research Fund, London, 1905, Part I, p. 49.

[3] "Further Observations and Experiments on Goitre (so-called Thyroid Carcinoma) in Brook Trout (*Salvelinus Fontinalis*)," *Jour. of Experimental Medicine,* Jan. 1, 1914, p. 70.

about the tenth month in this hatchery; that visible goitres usually manifested themselves about the beginning of the second year, though they may be present as early as the sixth month, depending on the favorableness of conditions for overgrowth, and progressively increased during the second and third years; that older fish were more resistant and tended toward spontaneous recovery; that the water in which these fish lived was not naturally goitre-producing, since fish living wild in the stream and raceways did not develop thyroid overgrowth.

"It was further shown that overcrowding and overfeeding with the highly abnormal and incomplete diet of hog's liver and heart were the major gross etiological factors, and of these the food was the more important factor in bringing about a fault of nutrition which stimulated the thyroid to compensatory overgrowth. No evidence was obtained that the disease was either infectious or contagious, or that a direct *contagium vivum* could account for the phenomenon."

He concludes his paper with the following statements:

"1. Goitre in fish is a non-infectious, non-contagious, symptomatic manifestation of a fault of nutrition, the exact biochemical nature of which has not been determined.

"2. Feeding the highly artificial and incomplete diet of liver is the major etiological factor in bringing about this fault of nutrition, which is at once corrected by feeding whole sea fish.

"3. Water plays no essential part in the etiology, transmission, or distribution of the disease in the fish of this hatchery."

It will thus be seen that the statements for which Dr. Gaylord and the New York State Laboratory have been responsible, and through which a great deal of needless anxiety has been caused, are by no means generally accepted, and in all probability are erroneous.

MOLLUSKS

Tumors in mollusks are presumably very rare; certainly recorded cases are not very numerous.

Williams[1] reported having found one tumor in 700 mussels examined. This was a pediculated tumor, about the size of a hazelnut, found on the internal aspect of the left pallial lobe of a fresh-water mussel taken from a private fish-pond at Hendon, Middlesex. He considered it an adenomyoma.

[1] Williams, Joseph W.—"A Tumour in the Fresh-water Mussel (*Anodonta cygnea*, Linn.)," *Jour. of Anat. and Phys.*, Vol. XXIV, 1889-90, p. 307.

Collinge,[1] Honorary Assistant Curator to the Conchological Society of Great Britain and Ireland, found two instances of tumor-formation in between two and three hundred specimens of mussels examined.

Ryder[2] reported the finding of a tumor in an oyster, the specimen having been presented to him by Professor Leidy. Neither Leidy nor Ryder, in the course of large opportunities for observation, had previously encountered such a specimen.

SUMMARY

The evidence is conclusive that tumors, benign and malignant, may occur in any multicellular animal organism. This discovery is of importance to the student of comparative pathology and to the investigator of cancer. It has opened the way for the laboratory investigation of many problems concerning cancer which, manifestly, can be studied only with difficulty in the human subject. The significance, for example, of age incidence, of sex incidence, and of heredity, the transplantability of cancer, and many other phases of the subject, have been elucidated in an important and remarkable manner in consequence of the discovery that animals other than man may suffer from cancer. Just what bearing this may eventually have upon the etiology of cancer remains to be seen. It certainly has not yet established any *essential cause* of the disease. It has not proved that man may acquire cancer through the consumption of animals afflicted with the disease. There is, therefore, no element of alarm, so far as the public is concerned, in the fact that no higher animal is quite exempt from some kind of tumor formation.

However, inasmuch as malignant neoplasms in animals are subject to degeneration and to mixed infection with organisms which may affect human beings, the careful inspection of all animals used for food is of importance.

[1] Collinge, Walter E.—"Note on a Tumour in *Onodonta Cygnea,* Linn." *Ibid.,* 1891, Vol. XXV, p. 154.

[2] Ryder, John A.—"On a Tumor in the Oyster," Proc. Acad. of Nat. Sciences, April, 1887.

CHAPTER III

GEOGRAPHICAL AND ETHNOLOGICAL DISTRIBUTION

Influence of Climate, Soil, Diet, and Habits of Life.—Inasmuch as one is more or less dependent upon another, and all are more or less interdependent, these factors may be discussed under one head.

It has been stated that cancer is much more prevalent in temperate than in hot or cold climates, and that it is entirely absent from frigid and torrid regions. This has been found, by late investigators, to be untrue. Those who have studied the subject of cancer among Esquimos, for example, have found it to be not entirely absent among these inhabitants of the far north. The natives of the South Sea Islands, of Equatorial Africa, and of other very hot countries, who were formerly thought to show an almost entire absence of malignant new growths, are now known to possess no such freedom. In Mexico, Central America, and South America, cancer is said to be of much less frequent occurrence than in North America, the frequency of its occurrence decreasing with the distance from the equator.

How much of these differences is traceable to a lack of observation and of reporting existent cases, further study alone must determine.

It is not probable that the climate, *per se,* causes whatever difference there may be. Some investigators hold, however, that it plays an important part in the production of conditions of life which seem to favor the development of cancer. With regard to the indirect influence of climate as it affects diet and habits of life, it has been pointed out that the greater variability of climate in temperate countries produces a more rugged people than either tropical or cold regions, and that this vigorous life calls for more active tissue change, which, in turn, creates the desire for more stimulating and nutritious food. This supposedly explains the larger consumption of meat in temperate climates, with the greater liability to dietary excesses, than are common to the hibernating natives of the far north or to the frugal and simple-living natives of the far south.

India is often cited as an illustration of the above contention with reference to the frugal life. It is said that millions of men live, marry, and rear healthy children upon an income which rarely goes above two shillings (fifty cents) per week, and is often less. It has been estimated that the 42,000,000 people of Great Britain consume, in food and drink alone, an amount equal to the whole income of over 300,000,000 of the people of India. In Great Britain the average weekly income is estimated as thirty-eight shillings ($9.50), and the meat consumption as 130 pounds per head per year, whereas the people of India, with their weekly income of two shillings or less, live on rice or millet, milk, butter, and vegetables, sparingly eaten. In consideration of these facts, it has been maintained, although the contention has not been established, that the manner of living must be a factor in the production of cancer.

In high-lying, dry districts, whether of temperate or tropical countries, cancer is said to be relatively less frequent than in low-lying, poorly drained regions, although exceptions to this statement may be cited.

In Kashmir, which is a high-lying valley, surrounded by mountains, and very largely inundated all the time, malignant and other tumors are not rare for India. From 1890 to 1899, inclusive, 2,000 natives were operated upon in the Kashmir hospitals for tumors, most of which were malignant.

Many other instances are cited by Haviland,[1] who maintains that the highest cancer mortality is found in low-lying districts, which are watered by rivers whose waters periodically flood the contiguous territory. He cites, as proof of his contention, the Thames and its tributaries, which traverse "a vast cancer field." The only localities in the Thames valley where the cancer mortality is low are those in which the subsoil consists of substances which readily absorb the water, such as chalk and oölite.

The Registrar-General's reports substantiate this view with reference to some sections of Great Britain, while with reference to others this does not seem to hold true.

Reviewing the influence of the various factors concerned in the geographical distribution of cancer, Williams[2] holds that the mortality from this disease is lowest where the struggle for existence is hardest, the density of the population greatest, the

[1] Haviland.—"Geographical Distribution of Disease in Great Britain." 1st edit., 1875; 2nd edit., 1892.
Also: "The Medical Geography of Cancer in England and Wales," *The Practitioner*, 1899, LXII, N. S. IX, p. 400.
[2] Williams W. Roger.—"The Natural History of Cancer," 1908.

tuberculosis mortality highest, the birth-rate highest, the average duration of life shortest, the infantile and general mortality highest, and where sanitation is least perfect. In other words, according to his findings, the cancer mortality is lowest among the poor of the industrial classes of the larger cities, and highest among agricultural communities, and among the prosperous and well-to-do of the cities. "High feeding and easy living" he holds to be the most potent factors in the causation of cancer. In other words, habits of life are given an important part in its production.

Exception has been taken to the numerical methods relied upon by Williams. His statements are not in keeping with certain recent investigations. The Imperial Cancer Research Fund[1] has called attention to the work of the German Imperial Colonial Office, as reported by the German Cancer Committee, from Samoa, German East Africa, German West Africa, and the South Sea Islands. Report on the material thus forwarded states that carcinoma is by no means rare, as is generally supposed, in these countries. The relative frequency, it is stated, cannot be determined, but "it is certain that no new growth occurs in Germany which is not also found in the natives of the Tropics, and no new growth occurs in the Tropics which is not found in Germany. . . . The apparent rarity of malignant new growths is to be explained by the fact that the natives with such tumours do not go to the hospitals, but avoid them and die unknown, and this is particularly the case for internal tumours."

"This agreement," comments Bashford, "in the results obtained independently through the investigations of the German Imperial Colonial Office and the Foreign, India, and Colonial Offices of this country, should go far to dissipate any lingering belief that European habits of life are primarily responsible for the occurrence of cancer."

Racial Immunity.—It has been claimed by some investigators that no race is immune from cancer, that it may be found among the savages of the jungles of Africa, the semi-civilized natives of the Orient, and the highly civilized inhabitants of occidental countries. Others have read into the statistical findings a partial or complete immunity among members of certain races or nations, the reason for this immunity varying with the particular views of the individual student of the problem.

Some are inclined to believe that there is an inherent quality in the tissues of certain races which renders them practically immune from cancer. Others hold that whatever immunity may

[1] Eleventh Annual Report.

seem to exist arises from the conditions under which the individuals live, and that changed conditions will bring about changes in the degree of immunity. Still others are of the opinion that no race is immune, and that closer studies of the diseases of apparently immune races will reveal the number of malignant growths increasingly large as the study is increasingly close.

It has been frequently asserted, and great importance has been attached to the statement, that cancer is relatively rare in India, Egypt, and other countries, and in aboriginal races generally. Yet, as we have seen, closer study has revealed cases of cancer where previously the disease was supposed not to exist, where there is little reason to believe that it could be traced to any possible contamination by outside races or nations, and where environmental changes were hardly sufficiently marked to account for its sudden occurrence. Sporadic cases have been reported from many sections where the aboriginal natives have previously been supposed to be exempt.

One of the examples of the relative immunity from cancer, so often cited, is furnished by Japan. The entire country has long been considered remarkably free from the disease, the peasantry of some sections being cited as examples of complete immunity. Yet, within the last few years, since Japan has made such rapid strides in medicine, as in other fields of endeavor, the increasing attention devoted to the study of cancer has revealed a state of affairs far from racial immunity. (See Section III, Statistical Considerations.) Japanese statistics for 1899-1903 gave the average death-rate from cancer as 0.49, which is higher than that of such countries as Servia, Hungary, and Spain. As the methods of statistical investigation improve, the disease in its various forms will doubtless be found to be much more frequent in Japan than is now suspected.

It is fair to assume that the same would apply to the inhabitants of various countries supposed to be relatively immune, such, for example, as China, Persia, Arabia, most of the sections of Africa inhabited by blacks, the various islands of the Pacific, the Esquimos, and the natives of other cold countries.

From the foregoing it may be concluded that racial immunity is relative and not absolute, and that mankind, wherever found and under whatever conditions existing, is susceptible to cancer to a greater or lesser degree.

The Influence of Environmental Changes in the Production of Cancer.—Those who have held to the belief that aboriginal peoples, uncontaminated by civilization and the changed conditions which it brings, are free from cancer, have been accustomed to cite, among others, the inhabitants of New Guinea and various other islands of the Pacific, particularly of the South Pacific. It is interesting, therefore, to review the investigations of the Daniels Ethnological Expedition, in 1904, as reported by Seligmann, in the Third Scientific Report of the Imperial Cancer Research Fund.

Studies were made, during eleven months, of pathological conditions among the inhabitants of New Guinea and its neighboring islands. The inhabitants of these islands, just emerging from the Stone Age, and so little contaminated by the influence of white people that they have none of the exanthemata except, perhaps, German measles, and among whom venereal diseases have scarcely made any inroads, are not, as it was formerly thought, entirely free from benign and malignant new growths, although such conditions are very rare among them.

Among the benign new growths found by the above-named investigators may be mentioned papillomata, fibromata, lipomata, osteomata, angiomata, and fibro-cheloid formations. Among the malignant tumors found were encephaloid cancer, sarcoma, epithelioma, and rodent ulcer with histological characteristics of malignancy.

It is interesting to note, in connection with these studies, that the natives of some of the islands were found to be peculiarly liable to chronic ulcerative and irritative processes, and that wounds, which are very common among them, never heal except by "second intention," every native past middle life having one or more scars of considerable size. These possible sources of irritation, therefore, were not considered as being, *per se,* sufficient to produce new growths.

It was also noted that the natives are free from gout, arteriosclerosis, and other conditions due to faulty metabolism, and, as we have already seen, that syphilis is practically absent. For these reasons old age is not accompanied by the retrogressive changes which are supposed very largely to be concerned in the production of malignant disease. The absence of gout and the other conditions named, among certain of the islanders, may be traced to the fact that they subsist exclusively upon vegetable diet. It does not necessarily follow, however, that this mode of life, as some maintain, accounts for the rarity of cancer among them, for the reason that the inhabitants of other neighboring islands, Australia, for example, live mostly upon animal food, being great hunters and poor gardeners, and yet both benign and malignant tumors are as rare among them as among their vegetarian neighbors.

From these studies Seligmann concludes that, in the rare cases of malignant disease occurring among the inhabitants of the various islands visited, the incidence of the disease seems to be associated in some obscure way with the adoption of a mode of life which simulates, to a certain extent, that of the white man. This would seem to substantiate the claim often made that aboriginal man is practically immune, and that the mode of living is an important factor in cancer incidence, environmental changes having much to do with the genesis of the disease. Just how far still further investigation will bear out Seligmann's findings remains to be seen. In the meantime it should be noted that the length of Seligmann's sojourn in New Guinea may not have sufficed to bring him into very intimate contact with the inhabitants of an island which is notoriously difficult of exploration.

It has been maintained by Williams that the chief physical difference between savage and civilized man consists in the latter being better nourished. He holds that cancer is of most frequent occurrence among prosperous, highly nourished communities, and, within the limits of such communities, to be commonest among the well-to-do. His theory is that this may be explained largely upon the basis of environmental changes, the greatest of which are urbanization and the enormous increase of riches and material prosperity. Sudden and marked environmental changes, as from the pastoral life of former times to the pent-up, crowded life which the majority of people now lead in the cities, he believes to be responsible for the increase in cancer in all occidental countries. The rapid encroachment of civilization upon savage territory, and the modifications, to a greater or less extent, of the methods of existence of the latter, are supposed to account, at least in part, for the increased susceptibility of savage races coming under the influence of civilization.

It has been shown by the Registrar-General's Reports that the lowest cancer mortality is found where conditions of life are hardest. Thus the rapid increase, within the last century and a half, of wealth and general material prosperity is cited as a causative factor in the increase of cancer in Europe and America.

The negro is often cited as one of the most striking illustrations of the influence of environmental changes upon cancer genesis. In his native African home, under the surroundings which for centuries remained practically the same, it has been thought, inferentially and perhaps incorrectly, that he was immune to malignant new growths. After two centuries of life under new conditions, as in the Southern States, the negroes no longer serve as examples of racial immunity. Whether or not this is due to a real increase in liability or to the results of improved observation will be considered later. (See Section III.)

It has also been maintained that the alleged racial immunity of the Jews is lost when they live under conditions which seem to favor cancer development among the non-Jewish people around them, although it is still maintained by some that they remain less liable under all conditions than are their Gentile neighbors. In this connection the reader is referred to statistics from the "Kosher Wards" of certain hospitals. (See Section III, p. 96.)

What has been said of negroes and Jews has likewise been stated with reference to the North American Indians.[1] They have become more susceptible, according to some investigators, to malignant diseases under their changed environment.

A great deal has been written to prove that this apparent increase in susceptibility is traceable to changes in diet, and a great deal more has been written to disprove any such claims. But as yet we have insufficient definite knowledge on the subject, especially before the changes of environment took place. A more extended study is called for in explanation of this alleged loss of immunity or increase of susceptibility under altered environment.

ILLUSTRATIONS OF THE UNIVERSALITY OF CANCER

INDIA

India has attracted considerable attention among the students of cancer. It appears an interesting field for investigation, because of its dense population and the poverty and abstemious methods of living of its natives. Particularly does it interest those who hold that cancer is a disease of overnutrition or other abnormal environment.

While it may be said that all varieties of malignant disease are found in India, certain features are presented, particularly with reference to type and site-incidence and the variations of these in different localities, some of which are cited below.

David W. Sutherland,[2] Professor of Medicine, Lahore Medical College, made a study of the cancer cases admitted to the

[1] Hoffman, Frederick L.—"The Menace of Cancer," Trans. Am. Gyn. Soc., 1913.

[2] Sutherland, David W.—"Statistics of Malignant Disease Admitted to the Mayo Hospital, Lahore, Punjab, India, from 1892 to 1903 Inclusive" Archives Middlesex Hospital, Third Report from the Cancer Research Laboratories, 1904, p. 84.

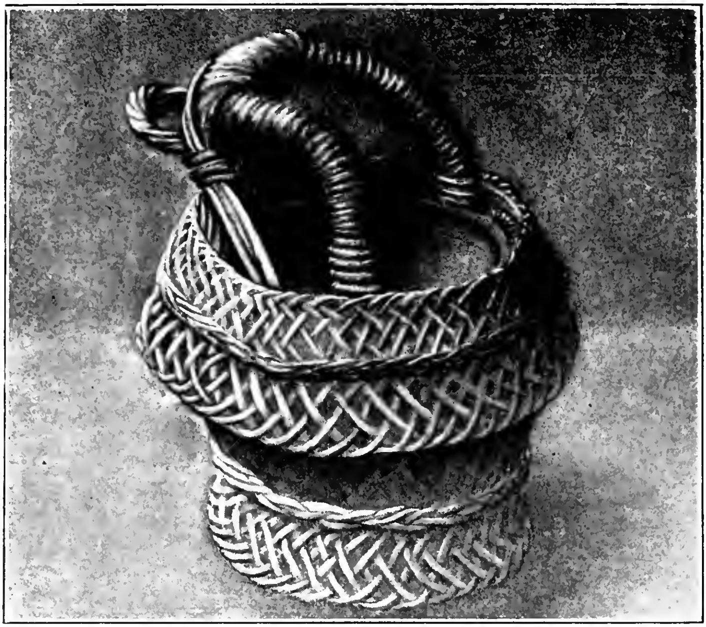

PLATE I.—Kangri Basket.

PLATE II.—Natives of Kashmir, in characteristic attitudes, using Kangri baskets. One, standing, is wearing a basket next to the abdominal skin. Two, squatting, have baskets between thighs and knees. These natives thus unwittingly furnish data concerning the production of cancer by chronic irritation, changing entirely the relative distribution of cancer of the skin as known in other parts of the world. (Enlarged from the Third Scientific Report, Imperial Cancer Research Fund.)

Mayo Hospital in Lahore, which draws its patients from all parts of the Punjab and, to some extent, from other adjacent states.

From these records he found, that of the total 43,412 cases admitted to the hospital during the twelve years from 1892 to 1903, 792 were cases of malignant disease. Of this number the classification, as given in the registers, was as follows: Carcinoma, 400; Sarcoma, 334; "Abdominal Growths," 35, and "Malignant Growths," 23.

From the statistics collected Sutherland concludes that they bear out the general principle that cancer tends to occur at the sites of chronic irritation where there is constant need for cell repair. Fifty-eight cases of epithelioma and thirty-six of rodent ulcer occurred in the skin, which in India is so universally the seat of injury because of the scanty clothing worn by the natives, and because of certain habits of life among them.

The Mohammedans, for example, shave the head as a whole, the Hindus in part, and the irritation from blunt razors is supposedly the cause of the large number of scalp cancers.

"Kangri Cancer"[1,2]—epithelioma of the skin of the front abdominal wall—is a common form among the natives of Kashmir, a province adjoining the Punjab. This is attributable to the Kangri burn, a long-continued irritation produced by the Kangri. The Kangri is a small earthenware vessel surrounded by basket work, used to contain a charcoal fire, and worn by the natives suspended from the waist, under the flowing robes and next to the skin, for the purpose of protecting them against the cold (Plates I and II). The prolonged irritation produced by this means very often eventuates in epithelioma of the skin, with metastasis in neighboring lymph glands.

Cancer of the penis is practically unknown among the Mohammedan population of India, presumably in consequence of the universal practice among them of circumcision, and the removal thereby of the element of chronic irritation produced by the accumulation of dirt and secretion under the prepuce, where circumcision is not practised, as among the Hindu part of the population.

Cancer of the lip, tongue, cheek, and buccal mucous membrane is of relatively frequent occurrence in both sexes in India, in consequence of the chronic irritation produced by

[1] Neve, E. F.—"Decade of Tumour Surgery in Kashmir Mission Hospital," *Indian Med. Gazette*, May, 1902, p. 164.

[2] Bashford, E. F.—"The Ethnological Distribution of Cancer," Third Scientific Report on the Investigations of the Imperial Cancer Research Fund, 1908, p. 1.

the chewing or holding in the mouth of a mixture of betel leaves, areca nut, tobacco, and slaked lime. This is supposedly analogous to the "clay pipe" cancer of other countries.

The tendency of cancer to effect the lower parts of the intestinal tract is supposedly traceable to the fact that the vegetarian diet of the natives calls for intestinal rather than gastric digestion.

GILBERT ISLANDS[1]

(British Archipelago in Oceanica)

Alexander Robertson,[2] M.B., C.M., Medical Officer Gilbert and Ellice Islands Protectorate, reports four cases of cancer in natives, as follows: scirrhus cancer of right breast in a female, 34; cancer of uterus, 28; cancer of lower lip, cheek, and tongue, male, 55; carcinoma of uterus, 40.

These cases were from Tarawa. He was unable to say whether malignant disease was prevalent in other islands of the group. He mentions two cases which had been reported to him. The first was epithelioma of the lip in a native of Ocean Islands, and the other carcinoma of the breast in a native of Union Islands.

ICELAND

Lazarus-Barlow[3] made a study of the occurrence of cancer in Iceland, as compared with its occurrence in Lahore, as reported by Professor Sutherland (*loc. cit.*).

The information obtained by Lazarus-Barlow was contained in reports furnished him by the Royal Board of Health in Copenhagen, and by Dr. Jonasson, First Medical Officer in Reykiavik.

From these reports it appears that Iceland has not been exempt from cancer, although the disease has always been, and still is, of uncommon occurrence in that country. It has been fairly evenly distributed over the country, and has been marked by the usual symptoms and sequences.

It seems, however, from the annual reports furnished to the Royal Board of Health at Copenhagen from about 1866 on-

[1] British Archipelago in Oceanica—16 small islands covering a total area of about 166 square miles. About 36,000 colored inhabitants, mostly uncivilized, but including a number of converts to Christianity. The group was discovered in 1765, and came into possession of Great Britain in 1892.

[2] Robertson, Alexander.—"Cancer in the Gilbert Islands," *Journal of Tropical Medicine,* November 1, 1905, p. 317.

[3] Lazarus-Barlow, W. S.—"A Note on Cancer in Iceland," Archives of the Middlesex Hospital, Fourth Report from the Cancer Research Laboratories, 1905, p. 273.

ward, that cancer was extremely rare in Iceland previous to the year 1896. About this time (1896) "unusually many" cases were reported. From 1890 to 1900, 115 cases were reported. Judging from the site incidence in these cases, carcinoma, rather than sarcoma, was the type of disease manifested, although the diagnoses were clinical, no microscopic or *post-mortem* examinations having been made. The population of Iceland during the decade mentioned ranged from 69,977 in 1890 to 76,308 in 1900. The number of cases of cancer reported during these years ranged from 2 in 1890 to 22 in 1900.

More than half the number of cases recorded were said to affect the stomach, only 20 out of the 115 cases involving other parts of the alimentary tract. The lip was involved in 13 cases, the tongue in 4, the face in 1, the esophagus in 5, the stomach in 58, the liver and stomach in 4, the intestines in 4, the rectum in 2, the uterus in 5, and the breast in 15 cases of the total 115.

The complete absence of cancer of the penis was noted as compared with its frequent occurrence among Hindus.

Compared with the records of the Middlesex Hospital, Lazarus-Barlow noted the relative frequency of cancer of the stomach and parts of the alimentary tract in Iceland, and the tendency of the disease to affect the *lower* parts of the alimentary tract in India.

SUMMARY

The influence upon cancer incidence of climate, soil, diet, and habits of life has not been proved. In other words, it has not been established that any of these factors are potent to absolutely prevent the occurrence of cancer. Extended study of the geographical and ethnological distribution of the disease tends more and more to show that no country, no district, no race, no nation may be considered as possessing immunity. The supposed freedom of savage and semi-civilized races is accounted for, at any rate in part, by the relatively small number of these individuals who have been examined, by age incidence, and by other factors not concerned with geographical and ethnological questions. There are no data which permit of an accurate comparison of the frequency of cancer in different parts of the world inhabited by the same race, for example, the Teutonic and Latin stocks in America and Europe, and the negro in Africa and in the United States. Similarly no comparison can be made between different races of mankind.

SECTION III

STATISTICAL CONSIDERATIONS

SIGNIFICANCE AND VALUE OF STATISTICAL STUDIES

Opinion concerning the importance to be attached to the application of statistical methods to medical problems has varied from time to time. At one time the value of statistics was grossly exaggerated. It was then supposed that by statistical methods alone it was possible to define the etiological relationships existing between phenomena occurring together or following upon one another. At another time statistics were greatly undervalued, or discarded altogether as yielding only ambiguous results. "You may draw any conclusion you like from statistics" was often the comment with which they were dismissed from serious consideration.

To-day, however, there prevails a more just appreciation of the proper value and legitimate application of statistics. Members of the medical profession are learning to differentiate between mere juggling with figures and really valuable statistical work.

It is only by collecting accurate statistics of illness or of death that the relative healthfulness of a country, a town, or a trade may be determined. And it is only by separating the different causes of death from each other, and stating them in percentages of the population, in what are known as "vital statistics," that the value of improved sanitation and other better conditions of living has been established, and that such practices have been generally promoted.

Statistical studies have contributed very largely to the advancement of knowledge concerning cancer in the past, and continue to do so to-day. All such matters as the zoölogical, ethnological, and geographical distribution of cancer are essentially statistical. The distribution of cancer in the two sexes; its relative frequency in different parts of the body; the ages most liable to it; the effect of climatic conditions, of soil, diet, alcohol, tobacco, and occupation; the influence of child-bearing, and the effects on women of their inability or refusal to suckle their offspring; the results obtained by surgical and other treatment—all are capable of statistical study from a theoretical point of view. From the practical point of view, however, many difficulties are encountered in such studies, in some instances insurmountable, and in others not yet surmounted.

DIFFICULTIES ENCOUNTERED IN THE COLLECTION OF STATISTICS

For acute diseases the collection of data and the compilation of valuable statistics are easy, especially if the disease attacks almost solely one period of life, for example, childhood; and if the two sexes do not require to be separately treated. With the increase in the duration of illness before death, the difficulty increases, especially if the liability be spread over many decennia of life, and if the two sexes have a different liability.

All of these difficulties are met in their highest degree in the case of cancer. In many countries and towns, where quite useful statistics are available for infectious diseases, such are still entirely unreliable or absolutely lacking for cancer.

The literature of the statistics of cancer is enormous but of very unequal value, and nowhere else does the bewildering conflict of fact and fiction appear to stand forth more prominently. Yet this bewilderment is chiefly due to faulty statistical methods, to tabulations of figures utterly unworthy of being styled statistics at all, and even to reliance on mere hearsay statements that cancer either occurs or does not occur under certain given circumstances. If it were frankly admitted that no reliable information is obtainable, and that, under many circumstances, the data on which accurate statistics could be based are not, and are never likely to be, available, there would be no occasion for much futile discussion.

Thus, wide currency has been obtained for the view that cancer is rare in Japan because of the native habit of frequent bathing, or because the Japanese are largely rice-eaters; that it is rare in Hindustan because of the vegetarian diet of many castes; and that it is quite unknown in uncivilized races remote from civilization.

The alleged rarity of the disease under any one or all of the above circumstances has been urged with equal vehemence, according to the widely divergent views held by extremists of one or another school of partisans, as "proof" that cancer has a parasitic or dietetic etiology. The goodly output of literature which has appeared in book and magazine form has obtained prominence in the newspapers for these extremes of opinion, and statements alleging the large increase of cancer among civilized peoples, and the widely divergent possibilities suggested for its development, have contributed not a little to the public alarm and dread of the disease.

UNIVERSALITY OF CANCER AS SHOWN BY STATISTICAL STUDIES

The investigations of the Imperial Cancer Research Fund have shown that the disease occurs among all races of mankind —among those not living in close contact with civilization as well as among those that are. Exemption is not conferred by any of the many diverse conditions of life found among widely separated and primitive aboriginal races. Contrary to what was formerly believed, the disease is frequent in Japan, India, Egypt, and China. Thus the ground has been completely cut from under the feet of the honest but visionary propagandists who have based their arguments upon the unsupported assertions that cancer did not occur in this or that portion of the globe.

POSSIBLE ERRORS IN THE COMPILATION OF STATISTICS

As regards the relative frequency of cancer in different races and in different parts of the world, there are absolutely no reliable data. It cannot be denied that the disease is much more frequently recorded in some countries than in others, but there our exact information ceases. It cannot now be stated whether the difference is merely a question of recording the disease, or whether the relative proportions of the two sexes and the respective ages attained by them do not largely contribute, because, except in a few European countries, these essential data are not forthcoming.

In different countries there are wide variations in the relative numbers of males and females, and also in the relative numbers of males and females living at each age-period. These variations in what is technically known as the age and sex constitutions of the several populations introduce fallacies when comparison is made by *crude death rates,* in which the deaths are simply stated as per 1,000 persons living at all ages, both sexes being thrown together. It is therefore necessary to calculate *corrected* death rates, in which allowance is made for these differences in age and sex constitution.

The Registrar-General of England has done this for all countries able to supply the necessary primary data. Unfortunately it must be admitted that America has been unable to supply satisfactory details, for which reason American statistics are omitted from the following table. The age and sex constitution of the populations of England and Wales at the census of 1901, has been adopted as the standard for comparison, and from it the following table is obtained:

Cancer.—Death-rates per 1,000 Persons Living, 1881–1910

Countries (Arranged in order of crude rates in 1901–5.)	Crude Rates						Corrected Rates		
	1881–1885	1886–1890	1891–1895	1896–1900	1901–1905	1906–1910	1906–1910	1909	1910
Switzerland	1.03	1.14	1.22	1.27	1.28	.....	.....	1.07	.....
New Netherlands	0.60	0.70	0.81	0.92	0.97	1.03	0.90	0.90	0.93
England and Wales	0.55	0.63	0.71	0.80	0.87	0.94	0.94	0.96	0.97
Scotland	0.54	0.62	0.69	0.77	0.85	.....	.....	1.00	.....
Austria	0.44	0.50	0.59	0.69	0.74	0.78	0.73	0.73	0.73
Ireland	0.38	0.43	0.49	0.58	0.69	0.79	0.64	0.65	0.68
New Zealand	0.30	0.42	0.52	0.59	0.67	0.72	0.81	0.82	0.84
Prussia	0.34	0.41	0.50	0.57	0.65	0.74	0.73	0.74	0.77
Australian Commonwealth	0.36	0.42	0.49	0.57	0.63	0.70	0.83	0.85	0.87
Belgium	.....	.....	.....	.....	†0.58	.....	.....	0.54	.....
Italy	.....	*0.43	0.44	0.51	0.55	.....	.....	0.53	.....
Spain	.....	.....	.....	.....	0.44	0.50	0.44	0.44	0.45
Hungary	.....	.....	.....	*0.30	0.39	0.44	0.43	0.44	0.45
Servia	.....	.....	*0.60	0.08	0.10	.....	.....	.....	.....

*4 years. †3 years.

Even with these corrections, as shown in the table, there are great variations in the recorded frequency of cancer for different European countries. Some authors lay weight on these differences and regard them as real; others hold that the differences are in the main merely an expression of the reliability of the statistics, and that as the amount of cancer diminishes so does the inexactness of the statistics increase. For some European countries statistics are available only for the towns.

FALLACIES IN AMERICAN METHODS OF COMPILING STATISTICS

In America the state of affairs is even worse. The international scheme for the tabulation of deaths is employed in practically all states. American statisticians have ably contributed to the development of statistical science in general, particularly in developing the plan of assorting data mechanically by the card system, but they have not been provided with cancer data upon which to work. Hence there are no reliable statistics concerning either the relative frequency of cancer in the past as compared with the present, or its relative frequency in different states, in different towns, or in town as compared with country districts.

Instead of the essential data of population—the relative proportions of the two sexes, and the numbers in the respective age groups of each sex being set forth and brought into relation with the deaths from cancer—we find the deaths classified according to months, or per 100,000 or 10,000 of population, or even per 1,000 deaths from all causes, as in the map compiled for the United States by McConnell and reproduced on page 76. Inasmuch as the season of the year has no influence on the death-rate from cancer, as it has on infective diseases, the classification of cancer deaths according to months is an error. The consideration of the two sexes together is likewise a great statistical fallacy. The methods employed by different states vary in other ways, but almost without exception in a direction contrary to that which would lead to improvement.

This deplorable state of affairs is often due to the system under which those responsible for the registration of deaths and the compilation of statistics are appointed. The result is seen in the production of mere worthless tabulations of figures, which cannot by any possibility be given the value of statistics. American methods and their results justified Bashford in stating, in New York in 1912,[1] that he knew more about the occurrence of cancer in the different native races of Ceylon than his audience did about cancer among the different races in their own city. His criticism has not been answered.

American statistics also suffer, as emphasized by Oertel,[2] from the rarity with which autopsies are performed. Oertel publishes figures showing how large a proportion of autopsies are performed in Europe, and other authors have demonstrated how high a proportion (20-40 per cent.) of deaths from cancer, especially internal cancer, are recognized, even in hospitals, only after an operation or autopsy is made. The well-known and deplorable difficulty of obtaining autopsies in America has its bearing upon many phases of medical progress, not the least of which is concerned with the compilation of reliable statistics with reference to cancer.

The unfortunate condition of the vital statistics of the

[1] "A Review of Recent Cancer Research."—The Middleton-Goldsmith Lecture, New York Pathological Society, October, 1912.

[2] Oertel, H.—"The Inaccuracy of American Mortality Statistics (with comment)," *American Underwriter*, Vol. XXXIX, May, 1913.

United States is described in the "Physicians' Pocket Reference to the International List of Causes of Death" (2nd Edition, 1913), which is issued to every physician in the United States by the Bureau of the Census, Washington, D. C. The first edition of this valuable booklet was sent out in January, 1911. The Director of the Census, William Harries, states in the preface to the second edition, that "it has been of great service in improving the quality of the returns of causes of death, and has further aided in showing the importance of vital statistics, of adequate legislation for this purpose, and of the thorough enforcement of existing laws." The second edition gives the map here reproduced (Fig. 1), showing the growth of the registration area by the addition of many fresh states in recent years, and enforces the need for carrying out the registration of births and deaths.

Although the booklet is issued to every physician in the United States, it is pointed out how grievously the law is ignored. Public opinion in the country requires to be aroused to the practical value of universal birth and death registration,

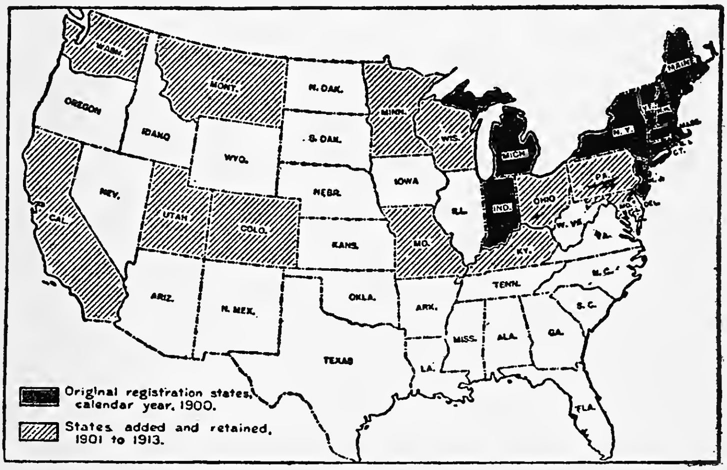

FIG. 1.—Map showing true state of American Vital Statistics in 1900.

if anything more than the rough computations of the deaths from cancer and other diseases is to be made available for the guidance of investigation.

The map given by McConnell[1] is also reproduced (Fig.

[1] McConnell, Guthrie.—"Die Krebskrankheit in den Vereinigten Staaten von Nordamerika," *Zeitschr. f. Krebsforschung*, 1908, Bd. VII.

2) for comparison with the map given by the Bureau of the Census showing the growth of the registration area for the United States. Comparison of the two maps shows that in 1900 only eleven of the many states indicated as giving cancer data in McConnell's map had joined the registration area. A

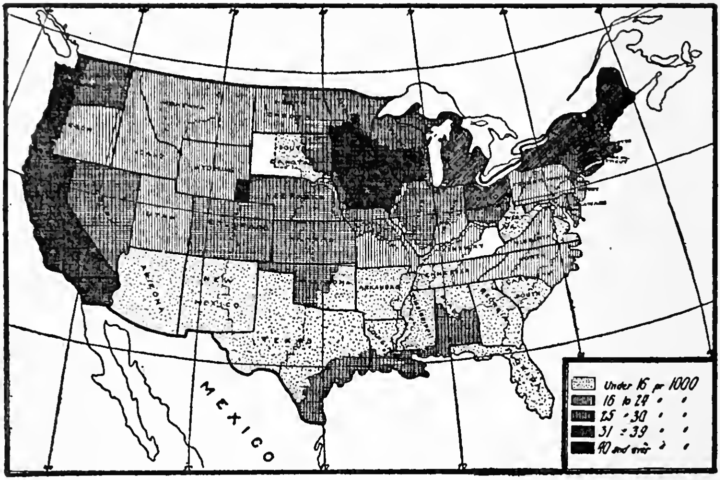

FIG. 2.—Map of McConnell reduced to same scale as above, giving by degree of black "the proportion of deaths from cancer per 1,000 deaths from *all* causes, in 1900." A comparison of the two maps shows that the facts in the first map prove that the second map has no value whatsoever.

moment's reflection shows how futile it is to attempt to establish the relative frequency of cancer in the several states in the present condition of American vital statistics.

IMPORTANCE OF AUTOPSIES IN THE COMPILATION OF CANCER STATISTICS

Bashford and Murray[1] point out the frequency with which malignant new growths present themselves at *post-mortem* examinations. The following table, giving the total number of autopsies and the total number of cases of malignant new growths for a number of years at a single hospital, namely Guy's Hospital, London, shows that on the average one case of malignant disease has occurred in every eight autopsies. It may be added that, as long ago as 1888, in 82 per cent. of the cases of malignant new growths thus presenting themselves, a microscopical examination is recorded.

[1] "The Statistical Study of Cancer," Second Scientific Report of the Imperial Cancer Research Fund, London, 1905, p. 41.

Year.	Autopsies.	Malignant.
1901	479	64
1900	457	76
1899	462	71
1898	449	58
1897	483	52
1896	536	63
1895	516	63
1894	495	61
1893	507	46
1892	478	62
1891	494	61
1890	494	49
1889	474	41
1888	467	49
Total for 14 years	6,791	816

One case in eight.

Reliable statistics of cancer require the collection of a large number of data having reference to the population as a whole, the relative numbers of males and females and the numbers in each age group for each sex. Accurate certification of the cause of death in every case can result only from uniform *post-mortem* examination, which is impracticable; but by insisting that the certification of cause of death must be made by a medical man, or that the body after death shall be examined by one, mortality statistics have been freed from many sources of fallacy.

FACTORS TO BE CONSIDERED IN CALCULATING CANCER DEATH-RATE

Age and Site Incidence.—The cancer death-rate must be considered according to age and stated in terms of the proportion of each sex living at each corresponding quinquennial or decennial age group. It is thus found, if all cases of cancer are taken together, that below 35 cancer is rare, but that it increases in frequency from that age to the end of life. There was long a fundamental difficulty in further analyzing this phenomenon because the official figures of different countries neither differentiated sarcoma from carcinoma, nor stated the different sites of the disease. For England and Wales this difficulty has been overcome, and a most interesting analysis made. The English Statistical Office responded to the emphasis laid upon the importance of incidence on different sites in the body, as shown by the comparison instituted by Bashford and Murray[1] between the age-incidence of cancer in short- and long-lived ani-

[1] *Ibid.*

mals, and by the fact that several organs of the human body have varied importance at different ages. The relation of mortality to age varies considerably for cancer of different organs, but little for the same organ in the two sexes.

If the uterus and breast be considered apart, the accompanying table, taken from the Report of the Registrar-General of England for 1909, shows that there is some one period of life, generally the same for both sexes, at which cancer of any particular organ is especially characteristic. Cancer of the face and lip have the mortality concentrated upon the extreme end of life, whereas cancer of the tongue has its maximum comparatively early.

England and Wales.—Cancer: Parts of Body, 1901–9.—Percentage of Deaths at Each Age-group to Total Deaths from Cancer in the Same Sex and Age-Group.

	0–35	35–	45–	55–	65–	75–	85 and upwards	All ages
Males								
Face	0.9	1.4	1.2	1.2	1.9	4.3	10.8	1.9
Lip	0.1	0.7	0.7	1.1	1.8	4.0	9.6	1.6
Stomach	8.7	20.9	21.5	22.4	23.1	20.2	12.8	21.4
Intestines	6.3	8.0	7.2	7.6	8.9	9.0	6.6	8.0
Rectum	7.1	8.6	9.0	10.4	11.1	11.4	9.9	10.2
Breast	0.1	0.1	0.2	0.2	0.2	0.3	0.5	0.2
Œsophagus	0.7	5.0	8.0	7.9	6.1	4.7	3.5	6.5
Liver and Gall Bladder	7.0	10.6	11.1	13.3	13.7	13.3	12.1	12.5
Bladder and Urethra	1.2	2.1	2.4	2.9	4.0	4.0	4.5	3.1
Tongue	0.8	5.5	7.7	6.2	4.7	4.1	3.2	5.5
Mouth	0.6	1.5	2.0	1.8	1.8	1.7	2.1	1.8
Jaw	2.3	3.0	3.5	2.9	2.6	2.8	2.0	2.9
Other Organs	64.2	32.6	25.5	22.1	20.1	20.2	22.4	24.4
Females								
Face	0.6	0.3	0.4	0.5	1.0	2.6	6.0	0.9
Lip	0.0	0.0	0.0	0.0	0.1	0.3	0.6	0.1
Stomach	6.0	8.9	11.6	15.4	18.0	16.5	11.2	14.2
Intestines	4.9	4.5	5.8	7.8	9.6	10.0	8.6	7.6
Rectum	5.4	4.6	4.9	6.1	6.8	7.2	6.0	6.0
Uterus	22.8	36.0	29.6	21.5	15.1	11.4	9.5	22.0
Breast	9.2	19.6	19.4	15.8	14.5	17.7	27.3	16.8
Œsophagus	1.9	1.8	1.4	1.3	1.6	1.7	1.3	1.5
Liver and Gall Bladder	5.1	6.9	10.5	15.2	16.8	15.7	11.2	13.3
Bladder and Urethra	0.3	0.5	0.6	0.9	1.2	1.5	1.5	0.9
Tongue	0.9	0.5	0.4	0.4	0.5	0.7	0.6	0.5
Mouth	0.4	0.2	0.1	0.2	0.3	0.2	0.3	0.2
Jaw	1.5	0.6	0.6	0.7	0.7	0.9	0.9	0.7
Other Organs	41.0	15.6	14.7	14.2	13.8	13.6	15.0	15.3

Sex.—The mortality figures for the principal cancers of the alimentary tract, stomach, liver, gall-bladder, and rectum, are seen from the table to be very similar in the two sexes; but in the male there is more cancer of the stomach and rectum, and in the female more of the liver and intestines. The liver occupies an exceptional position in both sexes, because most of the cancers occurring in that organ are secondary to cancer elsewhere in the alimentary tract—to cancer of the stomach, pancreas, intestines, and rectum in both sexes, and to cancer of the breast in the female. The period of maximum prevalence for the disease of the liver and stomach is from 65 to 75 and for the intestines and rectum from 75 to 85.

The table further shows that for males cancer of the stomach and, next to that, cancer of the liver, causes most deaths at each age-period after 35. Cancer of the rectum takes third place, except at the latest age-period, when cancer of the face causes rather more deaths. In women, as in men, apart from the reproductive system, the stomach and liver come first. The reproductive system holds an exceptional position for the female sex; the uterus is the principal seat of the disease up to 65, the stomach from 65 to 75, and the breast after 75. The total mortality from cancer of the uterus is much higher than that from any other organ in either sex, and more than half the victims are under 55 years of age. For cancer of the breast 40 per cent. are under 55. The table shows that in the first two age-periods for women, as many as 22.8 and 36.0 per cent. of all deaths of women from cancer are due to cancer of the uterus, whereas during this period cancer of the breast is causing only 9.2 and 19.2 of the total deaths. During the last two age-periods the position is reversed, uterine cancer showing only 11.4 and 9.5, as against 17.7 and 27.3 for mammary cancer.

For some organs there are two periods of maximum incidence. The table shows, with reference to the breast, that these periods are 35 to 55, and after 75, with an intermediate period at which the disease is less common in that organ than elsewhere. Bashford and Murray[1] had already directed attention to the occurrence of such a double fluctuation for sarcomata in general, there being a maximum at birth and another after 45, and also to the existence of a similar phenomenon for the curious mixed tumors of the kidney and adrenal.

An important point brought out by the table is the large percentage of deaths, viz., 64.2 and 41, which occur from cancer of other organs in the earliest period with a subsequent diminution for other age-periods.

[1] "The Statistical Investigation of Cancer," *loc. cit.*

OCCUPATIONAL MORTALITY FROM CANCER

The question of occupational mortality from cancer cannot be taken as settled. Newsholme[1] summarized the subject as follows, and recent years have added little that is new.

"The death-rates from cancer in men aged twenty-five to sixty-five, in each occupation, are stated as proportional figures, groups of men having the same proportion living at each age between twenty-five and sixty-five being compared, and the result called 'comparative mortality figures.' Thus stated, the number of males that would give 1,000 deaths in the general population in 1881-90 would give 47 deaths from cancer. Among all occupied males the comparative mortality figure from cancer was 44; among all unoccupied males, 96. Among clergymen and ministers cancer is represented by the comparative mortality figure 35, lawyers by 60, medical practitioners 43, commercial travelers 63, coachmen and grooms 58, seamen in the merchant service 60, dock and wharf laborers 51, porters 48, farmers 36, fishermen 46, maltsters 61, brewers 70, inn-keepers 53, inn-keepers in London 70, inn and hotel servants 65, tobacconists 51, fishmongers 42, grocers 34, drapers 49, butchers 57, shoemakers 50, tool, scissors, etc., makers 58, blacksmiths 45, plumbers 53, potters 35, coal miners 36, coal-heavers 56, gas-works service 59, general laborers 48, chimney-sweeps 156. The above have been selected from a much larger list. The contrasts are very striking and, in some respects, inexplicable. The theory that excessive nervous strain and anxious work provoke cancer does not receive support in the fact that the comparative mortality figure for medical men is only 43, while it is as high as 70 for brewers. The contrast between lawyers (60) and clergymen (35) is great; and although the latter may be supposed to possess an unusual amount of freedom from mental harass, the former, with their long vacations,[2] cannot be said to suffer exceptionally from such harass. Chimney-sweeps occupy a supremely high position in mortality from cancer. It would appear that the irritating effect of the products of imperfect combustion of coal is much more prone to bring out cancerous activity than the manipulation of the crude coal, though coal-heavers have a somewhat high propor-

[1] Newsholme, Arthur.—"The Statistics of Cancer," *The Practitioner*, April, 1899, Vol. LXII, N. S. IX, p. 371.

[2] Newsholme refers to England. The Royal Courts of Justice opened on October 13, 1913, after a recess of ten weeks, for another working "year" of some six months. There are long holidays at Christmas and Easter.

tional amount of cancer. The low cancerous figure for coal-miners indicates that they enjoy a comparative immunity from cancer as well as from phthisis. Can any reasonable hypothesis be framed to explain why the manipulation of coal underground should be so much less irritating than its manipulation above ground? Can it be that we have to look to intemperate habits as being a main factor at work rather than the particular occupation? The figures for commercial travellers, coachmen, seamen, brewers, maltsters, inn-keepers, and butchers certainly point in this direction. The figures for chimney-sweeps, appear, however, to stand in separate and independent category."

Statistics have since been published, giving the experience of some insurance societies, appearing to show that the idea of the prejudicial influence of alcohol may have some basis on fact, but it is still a moot point whether this is true or not. In the case of the alimentary canal, at any rate, this possibility has been practically established by the greater frequency with which males suffer from cancer of the upper half of the alimentary canal and stomach, especially in occupations prone to alcoholic indulgence, as well as by the custom of some insurance companies which make a distinction in the premiums paid by the total abstainer, and even by those who indulge moderately in alcohol.

As regards chimney-sweeps, there seems to be no doubt that their liability to cancer of the scrotum is directly attributable to soot. Butlin[1] has pointed out the different liability of chimney-sweeps on the continent of Europe where care is taken to preclude entrance of soot under the clothing, and where great cleanliness is observed. Whether the soot acts as a physical or a chemical irritant is not settled. Its relation to cancer is paralleled by the occurrence of warts on the skin in pitch and paraffin workers. The liability of such warts to malignant degeneration has led to special legislation in England. Of other well-defined irritants, mention may be made of the frequency of papilloma of the bladder in aniline workers.

All these exceptional accumulations of cancer on particular parts of the body are of the greatest etiological significance, and point to real differences in the frequency and distribution of cancer in different populations. Their importance is enhanced when considered together with the differences revealed by the investigations of the Imperial Cancer Research Fund in the distribution of cancer in primitive races as the result of

[1] Butlin, Sir Henry T.—Evidence given in "Report of the Departmental Committee on Compensation for Industrial Diseases," London, 1907.

the practice of customs which lead to irritation of particular parts of the body.

IS CANCER INCREASING?

The question whether or not cancer is increasing can only be briefly reviewed within the limits of this volume. In England almost as soon as statistics had developed sufficiently to show the effects of sanitary reform, i. e., toward the middle of last century, it became apparent that the statistics of mortality from cancer were not taking the same downward course as were those of mortality from epidemic diseases. With the establishment of this fact there was precipitated the long debate, which still continues, as to whether the increase in the number of deaths recorded from cancer is real or only apparent. The phenomenon is universal wherever statistics are available throughout the world.

The faddists who do not, or who cannot discuss the figures and statistics recording the apparent or real increase may be dismissed summarily. For the most part they accept the view of a real increase because it suits their propaganda against the consumption of tea, coffee, butcher's meat, or any other circumstance in diet or habits of life which happens to be their pet aversion. Their arguments would apply with equal force to the improved sanitation which the last fifty years has seen, or to the development of aviation, as being responsible.

As regards the consumption of meat—chilled or frozen meat being especially singled out for condemnation—it may be noted that the increase in the deaths recorded from cancer in England was apparent long before chilled or frozen meat reached that country in any quantity, or toward the end of the seventies of the last century.

The cooking of vegetables and fruits is blamed, but surely vegetables and fruits were cooked long before the increase of cancer revealed itself, and therefore cannot be held responsible. The number of deaths recorded among vegetarian castes in India, who were formerly alleged to be exempt, is not due to any change in their habits, but "because the disease has been looked for and found," as Bashford tersely puts it in the case of the mouse and the cow. What is there in the life of a mouse or cow to-day which differs from that of ten years ago when no cancer was known in the mouse and only the expert knew of a few cases in the cow, as contrasted with the thousands of cases now on record? In Japan, where the habits of the people generally have undergone no change as regards diet, the phenomenon of the increase of cancer presents itself also in their national statistics.

To turn to the serious consideration of whether the increase is real or not, on the one hand it is urged that the improvements in the certification of the causes of death and in the diagnosis of cancer do not suffice to explain the recorded increase. Many who hold this view also advocate that cancer is infectious. On the other hand, it is said that these factors do suffice to explain all the increase, since this is mainly an increase of internal cancer, and since it is much greater in men than in women, owing to female cancer being more readily accessible to complete clinical examination. If the increase were real, there is no apparent reason why it should affect men more than women. It is urged further that the increase affects mainly the higher age-periods. These features of the increase are brought out in the accompanying table from Newsholme,[1] and it is difficult to reconcile the facts with such hypothetical causes as the consumption of tea, coffee, meat, or cooked vegetables.

Death-rates from Cancer per Million Living in Each Age-period, 1861–70 and 1896.

Periods	All ages	0–	5–	10–	15–	20–	25–	35–	45–	55–	65–	75 and upwards
							MALES.					
Death-rates 1861–70	242	13	8	7	18	26	60	204	536	1,201	1,862	2,258
1869...	618	27	23	19	42	48	89	419	1,362	3,340	5,427	5,992
Percentage increase between 1861–70 and 1896........	155	109	192	175	137	86	49	106	154	179	177	165
							FEMALES.					
Death-rates 1861–70	519	13	7	7	16	32	161	669	1,530	2,291	2,791	2,786
1896...	901	32	11	11	30	42	175	933	2,308	4,187	5,686	6,539
Percentage increase between 1861–70 and 1896........	74	150	60	60	91	33	9	40	51	83	104	135

King and Newsholme[2] emphasized the necessity for considering the parts of the body separately, according as they are

[1] "The Statistics of Cancer," *loc. cit.*

[2] King, George, and Newsholme, Arthur.—"On the Alleged Increase of Cancer," Proc. Roy. Soc. of London, Vol. 54, 1893, p. 209.

accessible or inaccessible to physical examination. Bashford reinforced Newsholme's arguments, with the result that even this recommendation was improved upon, and the collaboration of the Registrar-General's Office and the Imperial Cancer Research Fund resulted in the tabulation of all the deaths from

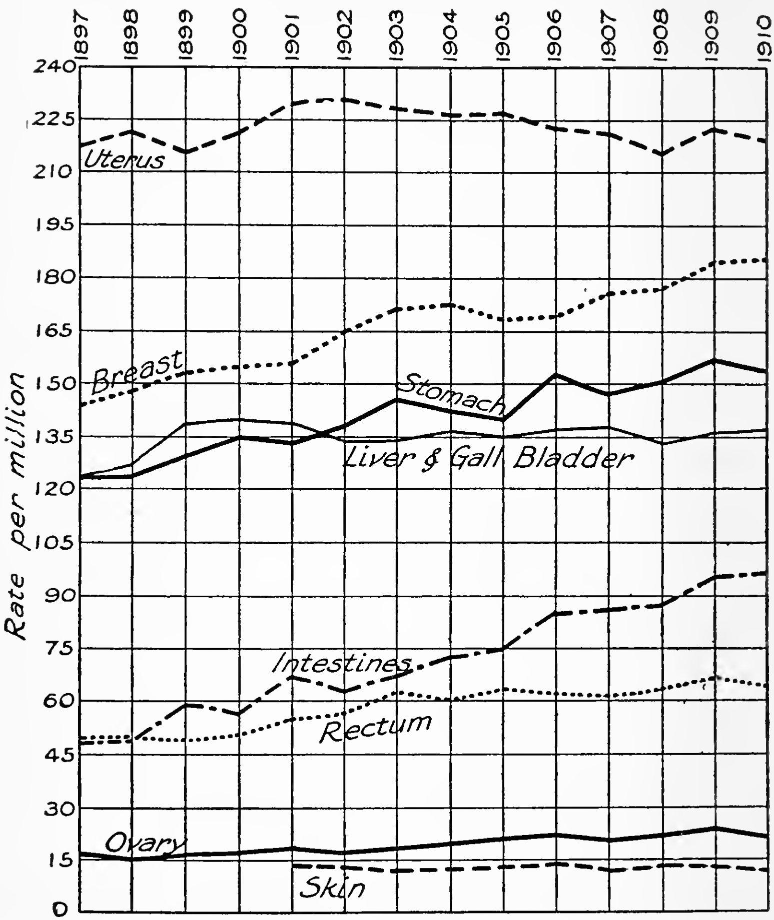

FIG. 3.—Analysis of cancer for women. Shows absence of increase for skin, uterus, ovary, liver, and gall-bladder, and increase for breast, stomach, intestines, rectum. (After Registrar-General for England.)

cancer for each single site separately for a period of ten years. In this way the enigma of the increase in the number of deaths recorded from cancer in general has been once and for all resolved into simpler problems for each part of the body. The table given on page 73 shows how baffling was the increase of cancer in general as contrasted with the simplicity of the problem presented by the two accompanying curves (Figs. 3 and 4) for separate parts of the body. The results have been summarized as follows:[1]

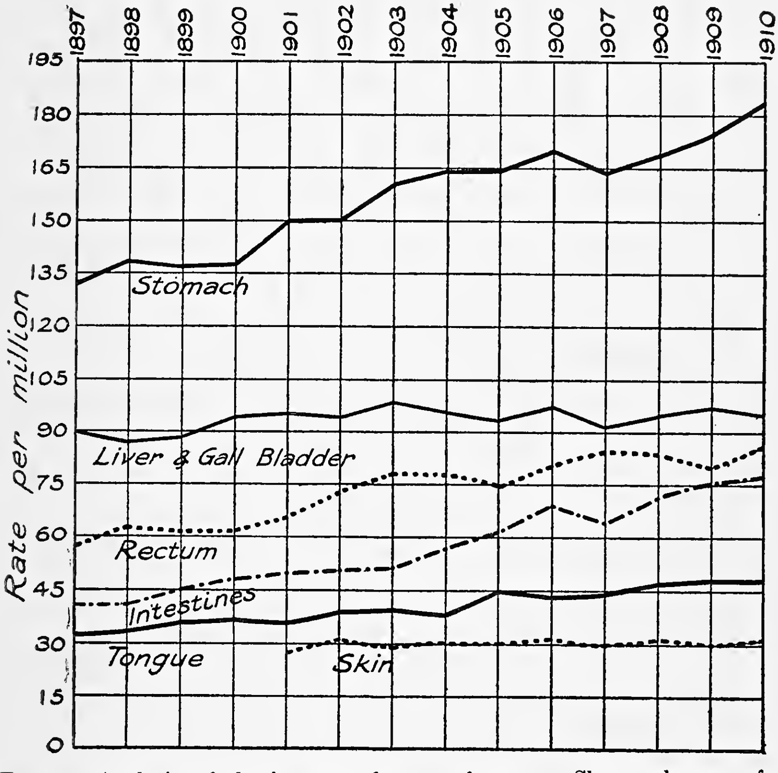

FIG. 4.—Analysis of the increase of cancer for men. Shows absence of increase for skin, liver and gall-bladder and increase for tongue, stomach, rectum, intestines. (After Registrar-General for England.)

"For several reasons it has long been desired[2] that the reports of the Registrar-General should contain detailed information on the incidence of cancer in different parts of the

[1] Introduction, Fourth Scientific Report of the Imperial Cancer Research Fund, 1911.

[2] The first serious attempt to attain this end was made by the late Sir Henry T. Butlin: "Proposed letter to the Registrar-General for England of Births, Deaths and Marriages on the subject of the increase of Cancer, drawn up by Mr. Butlin, of which the following is a copy," Proceedings of Council, *Brit. Med. Jour.*, November 12, 1887, p. 1070; King, George, and Newsholme, Arthur, "On the Alleged Increase of Cancer," *loc. cit.*

body, and Dr. Tatham was able to make arrangements for obtaining this information at the outset of these investigations. The application of the law of age-incidence of cancer to short-lived as well as to long-lived animals, reinforced the other reasons for obtaining it, and suggested that knowledge would be advanced by more detailed information about the age-incidence of cancer in the several organs of man as distinct from its dependence on the age-distribution of persons.[1] It was anticipated that the data would be of both biological and statistical value, and the facts published by Dr. Stevenson in the last report of the Registrar-General show that this hope has been fulfilled in several directions.

"The new tabulation of the data for the years 1901-09, for England and Wales has permitted an analysis being made of the figures recording the increase of deaths attributed to cancer, which brings out the fact that the increase during this period is referable to certain anatomical regions and not to others. Thus, for males the main increase falls on the alimentary tract, especially the stomach. The liver and gall-bladder and the skin show no, or only a slight, increase. For females the increase, although it falls mainly on the alimentary tract (stomach and intestines), affects also the mamma, while the uterus, ovary, liver and gall-bladder, rectum and skin show little or no increase. It is also of importance that the recorded mortality from cancer of the generative organs has not increased at the same rate as that for other organs, and that most of the increases affect the higher age-periods predominantly.

"*For the first time it is fully demonstrated that it is erroneous to make statements of a disquieting nature about the increase of cancer in general.* In conjunction with investigations[2] into the errors of diagnosis among hospital patients, means are afforded of determining, for parts of the body where the disease appears to be increasing, whether the increase is real or only apparent, and of ascertaining the causal factors peculiar to such parts. While it is evident that several of the differences brought out by the figures can be explained by more accurate diagnosis and by allocation of the seat of the disease from the secondary to the primary situations, as illustrated,

[1] Bashford, E. F., and Murray, J. A.: "The Statistical Investigation of Cancer," Second Scientific Report of the Imperial Cancer Research Fund, Part I, pp. 3, 24, and 51.

[2] Comparison of the clinical diagnosis with the results of pathological and microscopical examination. See Second Scientific Report of the Imperial Cancer Research Fund, Part I, pp. 18-24; Bashford, E. F.: Address on Cancer in Man and Animals. General Meeting of the XVIth International Medical Congress, Budapest, 1909, and in *The Lancet,* September 4, 1909, p. 694; *Berl. klin. Woch.,* 1909, Nos. 36 and 37.

e. g., by the relation revealed between cancer of the liver and gall-bladder and the alimentary tract, this may not account fully for certain other features. In particular, the increased incidence of cancer recorded for the mamma in women, and the tongue in men, requires further study and elucidation.

"The analysis also shows that the incidence is very unequally distributed among the several situations, indeed, that the whole curve of incidence may be different for different organs. A progressive increase up to the highest age-periods is characteristic of the face, lip, mouth, bladder, urethra, and breast only. The other organs show a distinct diminution in the highest age-periods; but it is not yet possible to determine whether this curve indicates a liability rising to a maximum and followed by a fall, or is merely the result of ascribing deaths to other causes in the case of cancer of internal organs in aged people. The proportion of total deaths ascribed to the ill-defined cause of old age is 65.6 per 1,000 deaths from all causes as compared with 65.7 for cancer, and it must be borne in mind that the increases recorded for cancer affect principally the higher age-periods, and that the average age of the population is increasing [see below]. Sufficient has been said to indicate how important are the problems which are solved or revealed by the improvement in the details given in the national statistics.

"The study of the occurrence of cancer in mankind, and in domesticated animals in widely separated parts of the globe, has shown that the practice of peculiar customs (involving the application of chronic irritants to particular parts of the body) provokes the disease in situations and organs from which it is absent when these customs do not obtain. It is reasonable to suppose that the frequency of cancer would be diminished if such practices as the use of the Kangri in Kashmir, chewing betel-nut in India, and eating very hot rice in China, were discontinued. It is also reasonable to assume that the introduction into England of these exotic customs would greatly increase the frequency of cancer in this country."

If the numbers living in 1881 at each quinquennial age-period be reckoned as percentages of those living at the same age-periods in 1911, see pages 88 and 89, obtained from the Census of England and Wales in 1911,[1] show that the proportion of the population in the cancer-ages was much smaller thirty years ago at all age periods except one. This phenomenon of itself will account for an increase in the abso-

[1] Census of England and Wales, 1911, Vol. VII. Ages and Condition as to Marriage. London, 1913.

lute number of deaths, although not for the apparent relative increase. (Fig. 5.)

Ratio of the Proportional Number Enumerated at Each Age-period in 1881 to the Corresponding Number in 1911 Taken as 100.

Ages	1881	1911	Ages	1881	1911
Under 5 years..........	127	100	45 and under 50 years...	83	100
5 and under 10 years...	118	100	50 and under 55 years...	89	100
10 and under 15 years...	111	100	55 and under 60 years...	88	100
15 and under 20 years...	106	100	60 and under 65 years...	99	100
20 and under 25 years...	102	100	65 and under 70 years...	86	100
25 and under 30 years...	92	100	70 and under 75 years...	88	100
30 and under 35 years...	84	100	75 and under 80 years...	91	100
35 and under 40 years...	82	100	80 and under 85 years...	92	100
40 and under 45 years...	87	100	85 and upwards........	83	100

In the most recent Report of the Registrar-General for England and Wales, that for 1911, published in 1913, the standpoint taken is summarized as follows:

"While the figures for a single year would be far too small a basis for forming a definite conclusion on this matter, and there is evidence pointing to a real increase of cancer of certain parts of the body (Report for 1909, p. XCIII), the figures for 1911 seem to harmonize sufficiently well with the hypothesis that recorded differences in mortality depend upon varying degrees of accuracy in diagnosis to make it worth while to watch those of subsequent years from the same point of view. If these latter point in the same direction, then we must ask ourselves whether England and Wales in 1911 do not compare with England and Wales in 1881 more or less as London in 1911 does with the rural districts in 1911. The peculiar history of the increase of cancer mortality in regard to age and sex would then be explained. The records show continuous increase at all ages for males, whereas in females the increase at ages 35-45 ceased about 20 years ago, and more recently that at 45-55. At the latter age-periods the increase still continues at rates which increase in rapidity with increase of age. The male increase at all ages would be explained by the fact that, taking the country as a whole, there is still considerable room for improvement in diagnosis at every age in males. The cessation of increase in middle-aged women is explained if we assume that cancer, being better diagnosed in the female sex and at the earlier ages, is now seldom overlooked in middle-aged females, although it formerly was so, the frequency of occurrence being assumed constant. Probably there is little doubt that cancer is more easily diagnosed, because more accessible, in females, but the assumption that it is more frequently overlooked in old than in middle age is more open to question. . . . It seems natural, however, that in the case of persons whose age alone suffices to explain failure of their vital

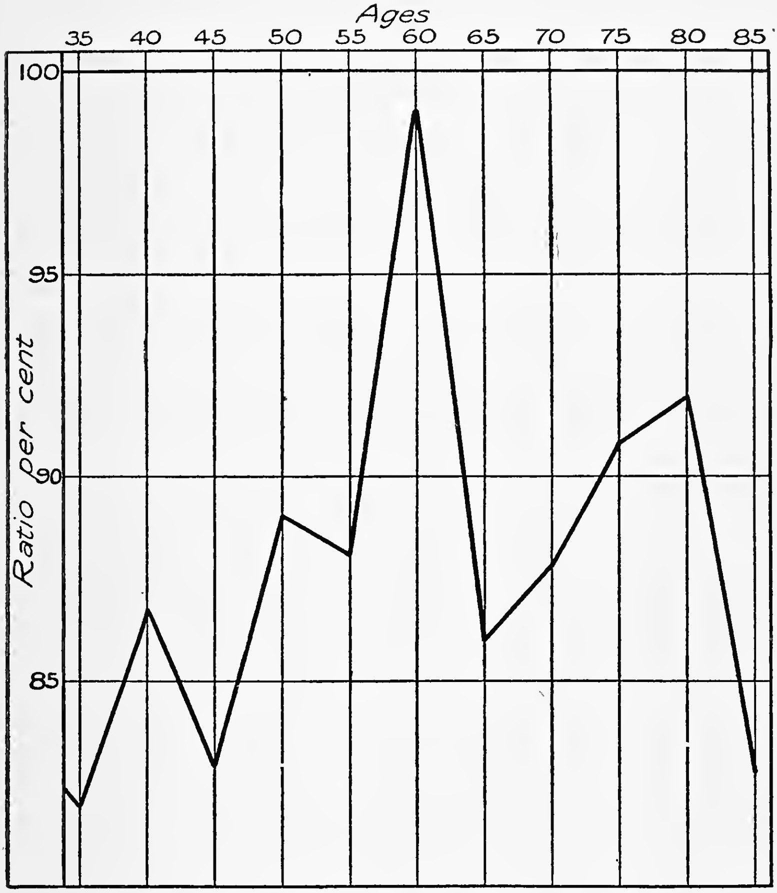

FIG. 5.—This chart indicates diagrammatically the increase in the age of the population of England and Wales. The year 1911 is here taken as standard for each age-period and is reckoned as 100 living for each age-period. The fluctuating line indicates how many were living in proportion thirty years earlier.

powers the search into the cause of obscure illness should at times be less rigorous than is felt to be demanded when a person of middle age is concerned, whose span of life is clearly cut short by definite illness of some kind."

It would thus seem that the long debate as to the meaning of the increase in the number of deaths recorded from cancer was to end by admitting the possibility of increase for some parts of the body, and in pointing very definitely to the lines along which statistical research may be pursued with profit. This result has been attained, not by compiling special statistics of cancer by means of a "cancer-census," but by improving national mortality statistics as a whole, and especially by considering those of cancer as an important part of all, as advocated and successfully carried through in England largely at the instigation of Bashford, and as the result of his arguments, based upon the comparative study of cancer in mankind and animals, and upon experimental investigations.

CANCER MORTALITY ACCORDING TO LOCALITY

The relative frequency of cancer in town and country calls for brief reference. Everywhere the diagnosis and treatment of disease and certification of causes of death, are backward in the country as compared with the towns. It is therefore not surprising that cancer is more frequently recorded in towns than in the country. That this may be largely the explanation is supported by the fact that it cannot be shown that overcrowding in the towns has any influence upon the death-rate from cancer. In all such questions of relative frequency in one area, as contrasted with another, the question of the relative proportions of each sex and the numbers of each living at the several age-groups is important. This fact was brought out some years ago by King and Newsholme [1] in a striking comparison between England and Ireland. The importance of the correction of cancer mortality for varying age-distribution of populations is particularly great when comparisons are made between different countries, or even between the different counties of England.

Comparison of Corrected and Uncorrected Death-rates.

Period	Not Corrected		Corrected	
	England	Ireland	England	Ireland
1860–66	498	553	625	614
1867–73	597	627	747	661
1874–80	719	680	911	699
1881–87	902	807	1,152	824
1888–90	1,091	894	1,393	912

[1] King and Newsholme.—"On the Alleged Increase of Cancer," *loc. cit.*

It will be observed that, by the uncorrected figures, Ireland stands a little above England for the first two periods, and a little below it for the other three, but that no very great difference appears between the rates for the two countries. The corrected figures, however, show that Ireland stands below England throughout, so that in the first two periods the position of the countries is reversed by the correction, and in the last three periods the difference in favor of Ireland is very great indeed. It is evident that the ordinary method of presenting statistics exaggerates the rate of cancer in Ireland as compared with England, a result which might have been expected, owing to the age-distribution of the populations of the two countries.

The fallacy here revealed when age alone is concerned—sex being left out of account—probably also invalidates all the statements that have been made as to the relative frequency of cancer in different states in America, and in different races, whether Indian, black or white, or of Teutonic, English, or Latin descent, more especially because persons are considered and no allowance is made for the relative proportions of the two sexes at the several age-groups. This criticism applies especially to the map (Fig. 2, page 76) which McConnell has constructed for America. This map is quite valueless because it is based upon a statement of the deaths in different state groups per 1,000 deaths from all known causes, which is well known to be a fallacious method. An epidemic of measles among children, for example, would upset the whole calculation by lowering the death-rate from cancer.

Hoffman[1] has recently published figures which he claims show the liability of the negro and white populations in the South, and a change in the liability of the negro population. These figures are not considered here in detail because the Census Bureau points out in the "Physicians' Pocket Reference" that the South has hitherto been entirely unrepresented by reliable state registration.

RELATION OF STATISTICS TO ETIOLOGY

It is well recognized that statistics should not be expected to prove the cause of any disease. They have often given important indications of the line of advance; they have likewise exploded fallacious views of etiology.

[1] Hoffman, Frederick L.—"The Menace of Cancer," *Am. Jour. of Obstetrics and Dis. of Women and Children,* 1913, 68, p. 88; Trans. Am. Gyn. Soc., 1913.

The late Doctor Roswell Park,[1] in an address before the International Surgical Congress, Brussels, 1908, summarized as follows his position with reference to the infectivity and treatment of the disease:

"Holding to these views, cancer must be treated much as we would treat a filth disease, especially when it has advanced to the ulcerative stage, namely by the most efficient cleanliness. Cremation should supersede earth burial, and all soiled dressings and discharges should be destroyed by fire, while rooms and even houses inhabited by cancer patients should be most thoroughly disinfected, both during illness and after death."

These statements did not meet with any response from the Congress, but their echo has reached the American public, and such views have been widely spread among the ignorant, leading them to demand that all furniture, bedding, etc., be burned.

A moment's reflection on what statistics have proved for the infective diseases, or, to use the exact term, "filth diseases"—if typhus fever be taken as the filth disease *par excellence*—shows that sanitation has effected their marked reduction, and in the case of the typical filth disease, typhus fever, its extinction, except where filth still obtains. This diminution in the infective or filth diseases has not been shared by cancer. It follows, therefore, that cancer conforms to other laws than those governing the occurrence and spread of filth diseases in the community.

It should not be inferred, of course, that disinfection should not be practised for the sake of cleanliness, and for the purpose of allaying the fears of the timid; but only that those forms of disinfection which are efficacious for dangerous infective diseases, such as smallpox, should suffice to overcome any reasonable or unreasonable anxiety.

Statistics dispose in yet another way of alarming statements such as the one quoted from Park. The enormously overcrowded and filthy conditions obtaining in parts of New York and London might be expected, in accordance with this view, to be hotbeds for breeding cancer, but there is no evidence of this being the case. Unfortunately there are no actual statistics which can be quoted for New York, but extremely valuable statistics are available for the different parts of London. The highest cancer death-rate occurs, not in the slums of Whitechapel, but in Hampstead, the highest lying suburb in London and the wealthiest residential section of the city, consisting of

[1] Park, Roswell.—"The Nature of the Cancerous Process," *II Congrès de la Société Internationale de Chirurgie,* Brussels, Sept. 21-25, 1908, Vol. II, pp. 321 and 338.

large villa residences in private grounds. There is no support found here for the view that the overcrowded tenement is more cancer-ridden than the mansion. The statistics directly refute any relation between overcrowding-filth and a higher incidence of cancer. Again, New York must be passed over, for there are no available figures. In Vienna,[1] Stuttgart,[2] and London [3] the relation between cancer and overcrowding has been carefully investigated, and for all three it could not be shown that overcrowding had any effect—indeed, in London there was more cancer in the least densely populated areas.

In view of such facts as the above the public has a right to demand that they shall not be made unduly anxious by wild and exaggerated statements, and in this demand they are supported by the effects resulting from alarming prophecies like the following, also made by Roswell Park, in 1899:[4]

"If for the next ten years the relative death-rates are maintained we shall find that ten years from now, viz., 1909, there will be more deaths in New York State from cancer than from consumption, smallpox, and typhoid fever combined."

Apart from the fact that this way of putting the data is not permissible in connection with accurate statistics, the subsequent course of events has not confirmed this prediction for New York State,[5] and it is hoped that in future prophecy will be abandoned as a weapon in scientific controversy, and that the public will consider the impartial tribunal of statistics to be more reliable than exaggerated assertions.

Another aspect of this same subject is raised by statements concerning "cancer houses," the occurrence of cancer in husband and wife—so called *cancer-à-deux*—and the risk of in-

[1] Rosenfeld, Siegfried.—"Kritik bisheriger Krebsstatistiken Mit vorschlägen für ein zukünftige Oesterreichische Krebsstatistik," Wien and Lpz., Vienna, 1911.

[2] Weinberg and Gastpar.—"Die bösartigen Neubildungen in Stuttgart 1873-1902," *Zeitsch. f. Krebsforschung*, Bd. IV, 1906, p. 18.

[3] Annual Report of the Public Health Committee of the London County Council, 1908.

[4] Park, Roswell.—"A Further Inquiry into the Frequency and Nature of Cancer," *The Practitioner*, 1899, Vol. LXII, N. S. IX, p. 385.

[5] The total deaths in New York State from pulmonary tuberculosis (consumption), smallpox, typhoid fever, and cancer, for 1899 and 1909 (as given in the 13th Annual Report of the State Dept. of Health, 1909, Vol. I, pp. 177-178) are as follows:

	1899.	1909.
Pulmonary tuberculosis	13,412	13,996
Smallpox	21	4
Typhoid fever	1,604	1,315
Total	15,037	15,315
Cancer	4,533	7,060
Difference	10,504	8,255

fecting the unborn babe because the grandmother is dying of cancer. The writer has failed to find any reliable statistician who supports the risk of infection in these ways. This is not surprising, in view of the fact that the large figures available for populations are now forsaken for the small figures of individual experience. The fallacies of small figures are notorious, and the risk of their creeping in is enhanced, in the case of cancer, by the fact that ultimately it kills 1 in 7 women and 1 in 11 men above the age of 35. With so high an average frequency in the general population, in accordance with the law of probabilities, accidental exaggerations of cancer statistics are to be expected. This chance will be enhanced whenever the circumstances are such that many persons in a given locality attain the cancer-age or to old age, as in the case of occupants of old family mansions, of agricultural districts, or districts selected for habitation by those retiring from business. To have any significance they would have to occur with great frequency instead of the great rarity with which they are actually recorded.

As regards contact—even less remote than that of a grandmother with her unborn grandchild—the figures for density of population deprive it of all significance, as indeed also do the negative results of experiments directly conducted with this possibility in view. That real accumulations of cancer do occur is not denied; it is only stated that reliable evidence—reliable from a statistical point of view—of contact being responsible does not exist. Even the actual handling of cancer, as practised daily by the surgeon and the hospital nurse, has been found to have no risks for either. Nevertheless, should a surgeon accidentally receive an injury at an operation, the observation is not infrequently at once offered, "I hope it was not a case of cancer," as happened to the author on his being attacked by blood-poisoning through a prick received while operating for appendicitis.

All these evidences of alarm on the part of the public are directly traceable to rash or careless statements, apparently with a statistical foundation, that cancer is a pestilential disease, or that it has been proved to be infective.

This idea is carried much further by laymen, with some of whom the notion is deeply rooted that cancer is allied to syphilis. The belief even obtains that cancer never develops without being preceded by syphilis. Anyone may call to mind noble individuals on whom no such suspicion could rest, and the occurrence of cancer in animals, among whom syphilis is unknown, demonstrates its absurdity. Nevertheless, an instance may be cited in which a happy family, in one of whose members cancer appeared, was inflicted with the unnecessary additional misery caused by the assertion of a college-trained girl to the effect that in all cases of cancer, syphilis must have preceded its appearance. The effect of such indirect imputations of immorality is disastrous. They are directly traceable to persons handling figures whose statistical significance or worthlessness they are unable to appreciate. Especially is this effect seen in the desire to falsify death certificates of prominent or rich people, in order to conceal the fact that cancer was the cause of death. Under pressure from the relatives many deaths from cancer are doubtless returned as from some other cause. Even among the poor, especially in America, cancer is considered as loathsome a disease as leprosy, and the dread of having the truth disclosed often leads to the refusal, by rich and poor alike, of autopsy. Thus the alarm of the public, arising from statements claiming to have a statistical basis, but in fact having no such foundation, contributes largely, in its turn, to the invalidation of statistics.

A final illustration of another popular fallacy, kept alive by figures quoted by dietetic enthusiasts, may be referred to in this connection, namely, that Jews, particularly orthodox Jews, never suffer from cancer. The statement is supposed to have a statistical basis, but in reality has none at all, such statistics as are available proving exactly the opposite. The idea originated, no doubt, in the biblical classification of the pig as an unclean animal; indeed, those who declare the exemption of Jews from cancer generally direct attention to the consumption of pork by Christians. There are more Jews in New York than there are in all Germany, but there are no statistics available which would show their relative liability. For Berlin the deaths are classified according to religious confession, but unfortunately no statement is made as to the relative frequency of causes of death in the separate confessions. The author, however, has had the opportunity of operating for cancer upon many Jews. In one instance the patient, who had sarcoma, was the young daughter of a Rabbi, regarding whose orthodoxy there could be no question. This case attracted considerable attention, showing how widely spread is the belief that Jews are exempt.

Theilhaber [1] has published figures from his clinic in Munich

[1] Theilhaber, F.—"Zur Lehre von dem Zusammenhang der Sozialen Stellung und der Rasse mit der Entstehung der Uteruscarcinome," *Zeitsch. f. Krebsforschung,* Bd. VIII, 1909, p. 466.

recording some cases in Jews. Sir Frederic Eve[1] has provided figures of the operations for cancer on Jews in the London Hospital, where provisions are made for orthodox and unorthodox Jews, there being actually a "Kosher" kitchen in that institution. Finally the attempt has been made to show that cancer is less frequent in Jews than in Christians in Amsterdam; but the figures, while demonstrating that cancer is by no means uncommon among the Jews of that city, are too small to permit of a comparison, nor has any attempt been made to separate the orthodox from the unorthodox, by which means alone the effect of diet and alcohol could be determined by the comparison of these cases with those of Christians.

The following tables, compiled by the author from the records of the London Hospital in the summer of 1913, is interesting in this connection. Unfortunately the ages of the patients had not been obtained, and it is impossible to say to what extent this factor modifies the relative frequency of cancer in Jews and Gentiles in this hospital.

Hereditary influence is another problem that statistics have been called upon to solve. Every surgeon knows of cases in which, after operating on the mother, a lapse of years has found him performing the same service for the daughter, or for some other near relative. Many would be satisfied with these facts as evidence of the influence of heredity. This conclusion by no means necessarily follows.

Percentages of Carcinoma Cases Admitted to London Hospital in the Year 1911.

Males:

Total admission	5,658
Gentiles	5,444
Jews	214

Among the 5,444 Gentiles there were 278 carcinoma cases, or 5.1 per cent.
Among the 214 Jews there were 7 cases of carcinoma, or 3.3 per cent.

Females:

Total admission	3,681
Gentiles	3,408
Jews	173

Among the 3,408 Gentiles there were 212 carcinoma cases, or 6.2 per cent.
Among the 173 Jews there were 11 cases of carcinoma, or 6.4 per cent.

Females Admitted under Gynecological Department:

Total admission	803
Gentiles	699
Jews	104

Among the 699 Gentiles there were 60 cases of carcinoma, or 8.6 per cent.
Among the 104 Jews there were 3 cases of carcinoma, or 2.9 per cent.

[1] Eve, Sir Frederic.—Personal communication.

Detail Report of Total Number of Carcinoma Cases, Together with Columns Showing Number of Jews in Each Group.

	Gentiles		Jews	
Site	Males	Females	Males	Females
A = Abdominal.				
Appendix	0	1	....	....
Colon	30	28	....	1
Pancreas	4	6	1	0
Peritoneum	5	8	1	0
Rectum and Anus	39	19	....	2
Stomach	31	21	4	0
Various	5	3	....	1
Total	114	86	6	4
	Total males, Jews and Gentiles.			120
	Total Females, Jews and G'tiles			90
B = Genito-urinary System.				
Bladder and Kidney	16	9	0	1
Penis, Prostate, Scrotum, and Testicle	21	....	0	....
Ovary, Uterus, and Vagina	....	8	....	0
Total	37	17	0	1
C = Upper Alimentary Tract.				
Lip	19	0	1	0
Mouth and Cheek	18	1	0	0
Tongue	28	1	0	0
Œsophagus	34	2	0	1
Various	10	4	0	0
Total	109	8	1	1
D = Breast.				
Breast	1	90	0	5
E = Various.				
Various	17	11	0	0
Totals.				
A	114	86	6	4
B	37	17	0	1
C	109	8	1	1
D	1	90	0	5
E	17	11	0	0
	278	212	7	11

All the difficulties raised by the great average frequency, when using associated cases as evidence of infection, arise here again even in an enhanced degree. Pedigrees constructed for many generations awake mistrust, owing to the greater uncertainty of the cause of death as given one hundred, or even fifty, years ago, and because it is not granted to us personally to observe completely more than one generation of the human race.

Hence directly contradictory views have been held in the past by equally competent authorities. Sir James Paget[1] believed that heredity was responsible in as many as 26 out of 160 cases, or one-sixth, and was "disposed to hold that it is not possible to conceive the origin of cancer, or of any disease of

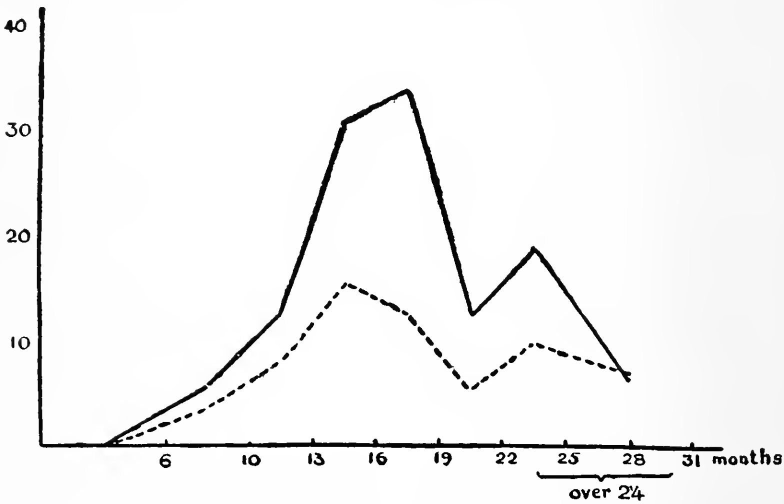

FIG. 6.—Percentage of deaths from mammary carcinoma to deaths from all causes at successive 3-monthly age-periods in female mice of recently cancerous ancestry (mother, grandmothers) ———, compared with the same ratio in female mice having more remote cancerous ancestry (mother and grandmothers non-cancerous) --------.

the kind, except by inheritance."[2] Roger Williams[3] and Sir Henry Butlin[4] have more recently claimed importance for it, but equally recently Bashford[5] and Weinberg[6] have given

1 Paget, Sir James.—"Lectures on Clinical Pathology," Vol. II, London, 1853.

2 Quoted by Harrison Cripps.—"Cancer of the Rectum," London, 1880.

3 Williams, Roger.—"The Natural History of Cancer," N. Y., 1908.

4 Butlin, Sir Henry T.—"Discussion on the Influence of Heredity on Disease," Proc. Roy. Soc. of Med., London, November, 1908, Vol. 2, R.S.M., p. 75.

5 Bashford, E. F.—"Heredity and Cancer," Proc. Roy. Soc. of Med., London, November, 1908, Vol. 2, R.S.M., p. 63.

6 Weinberg, W. and Gastpar.—Bösartige Neubildungen in Stuttgart," *Zeitsch. f. Krebsforschung*, Bd. II, 1904, p. 195.

elaborate figures from which they were unable to deduce proof of its influence for the human subject.

These statistical difficulties led to a resort to experiment, and finally experiments, interpreted by the aid of statistics, have demonstrated, in the case of mice, that an hereditary influence does obtain. Hence the lengthy disputations on this subject may be passed over.

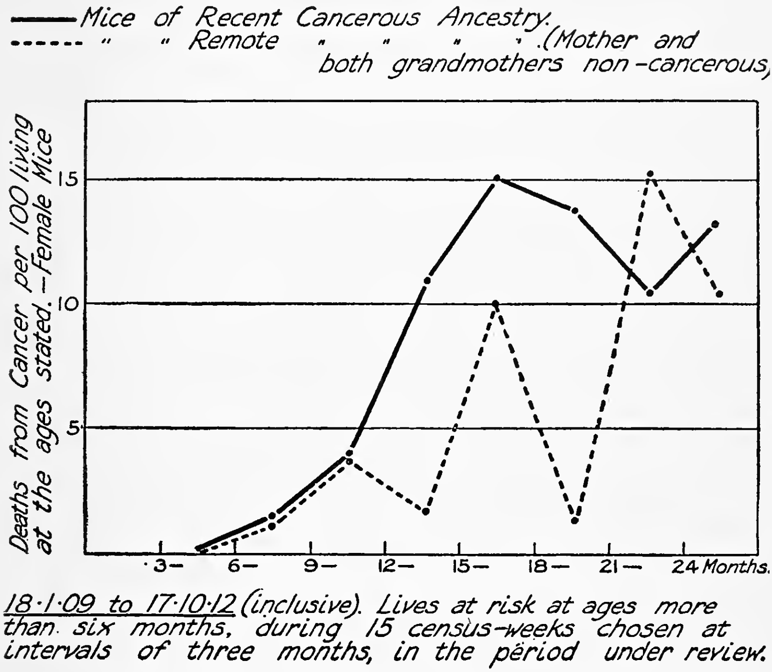

FIG. 7.—Curves showing the death-rate from cancer. Stated in this way the figures correspond to human mortality statistics. There is still a higher incidence in mice of cancerous ancestry. (After Murray, Proc. of International Medical Congress, London, 1913.)

For some years experiments on inbreeding cancerous mice led to negative results, but ultimately Murray[1] was able to obtain positive findings, and to confirm these by prolonging the experiments over many years. Murray's findings are briefly set forth in the following tables, for which also the accompanying curves (Figs. 6 and 7) have been constructed, one of them giving the latest results.

[1] Murray, J. H.—"Cancerous Ancestry and the Incidence of Cancer in Mice," Fourth Scientific Report of the Imperial Cancer Research Fund, London, 1911, p. 114.

Table I. (24th October, 1910). Female Mice of recent cancerous Ancestry. (Mother, one or both grandmothers, or all three cancerous.)

Age (months)	0–3	–6	–9	–12	–15	–18	–21	–24	Over 24	Total
No tumour.										
Living	....	....	9	7	6	8	7	4	6	47
Dead	....	....	49	48	39	28	22	20	18	224
Tumour Mice.										
Organs other than mamma	....	....	....	1	2	2	1	....	1	7
Mamma	....	....	4	7	15	18	10	5	3	62
Total	....	....	62	63	62	56	40	29	28	340
Per cent	....	....	6.5	11.1	24.2	32.1	25.0	17.2	10.7	18.2

Table II. (24th October, 1910). Female Mice of remote cancerous Ancestry. (No cancer in mother or grandmothers.)

Age (months)	0–3	–6	–9	–12	–15	–18	–21	–24	Over 24	Total
No tumour.										
Living	....	....	7	....	1	2	9	5	15	39
Dead	....	....	30	37	24	28	19	17	6	161
Tumour Mice.										
Organs other than mamma	....	....	....	....	....	....	1	1	2	4
Mamma	....	....	1	4	1	8	0	3	2	19
Total	....	....	38	41	26	38	29	26	25	223
Per cent	....	....	2.6	9.8	3.8	21.6	0.0	11.5	8.0	8.6

These breeding experiments show distinctly that in the case of mice the occurrence of cancer of the mamma in the mother or grandmothers increases the frequency of cancer of that organ by almost 10 to 15 per cent. at certain age-periods, especially the earlier age-periods. Equally accurate knowledge is not obtainable for the human subject owing to the greater length of life and the impracticability of always obtaining an autopsy and a histological examination. In the light of the results of these experiments the question arises as to the importance attaching to those rare family histories with an exceptionally high incidence of cancer. Family histories like the following are certainly very remarkable: "A man, one of a family of nine, died of cancer of the liver, the others being all alive and well. The patient's mother was one of a family of thirteen, seven of whom (four males and three females) died of cancer. Two died of cancer of the bladder, two of cancer of the liver, and one each of cancer of the throat, uterus, and breast. The patient's father died of diabetes, but his sister (the patient's paternal aunt) died of cancer of the bowel. Again, five members (four males and one female) of a family of nine children died of cancer. The four males died of abdominal growths and the female of cancer of the uterus. The mother and mother's brother also died of cancer; the father died of phthisis. The son of the eighth son died at the age of 28 of cancer of the bowel."

To these histories Bashford[1] added the following comment at a time when the breeding experiments in his laboratory were still yielding negative results: "Family histories of this kind are, however, rare, in proportion to the number of individuals attacked, and they are mainly of interest as showing that if cancer be transmissible by heredity, then transmission takes place both through the male and the female, without anything corresponding to what is known for hæmophilia and colour-blindness. These histories are so infrequent that they cause no surprise when the table of the relative frequency of cancer in the general population given above is considered; for, did these forms of family history imply hereditary transmission, then we should be able with ease to obtain tables of a hundred families in which the figures for no deaths, one, two, three, or more were the inverse of what they are in the population; but this is not the case. The isolated instances recorded in the literature serve only to show how rare this phenomenon really is. When recorded, it is more than probably to be looked upon as what would be expected to happen in the case of so frequent a cause of death as cancer, from a consideration of the distribution theoretically calculated according to the law of probabilities."

Raymond Johnson and Lawrence[2] give the following recent experience: "Among 500 consecutive cases of carcinoma of the breast treated in University College Hospital, there was a family history of malignant disease in 81, and in 37 of the 81 cases the disease was stated to have been in the breast. In one of this series of cases the patient's mother and her sister died from cancer of the breast, and the father's sister from cancer of the mouth; of the patient's sisters, 2 died from cancer, 1 of the stomach and 1 of the breast. If heredity plays any important part in the causation of the disease, it might be expected

[1] Bashford, E. F.—"Heredity and Cancer," *loc. cit.*

[2] Johnson, Raymond, and Lawrence, F. W. P.—Article on Tumors, in "A System of Surgery," edited by C. C. Choyce, Vol. I, p. 470.

that it would lead to its incidence before the average age. In this connection it may be stated that among the 500 cases of cancer of the breast referred to above, the average age at which the disease was first noticed was 49.62 years, whereas among the 81 cases in which any evidence of heredity could be traced, the average age was 48.74 years. The difference in this series of cases is so small as to be negligible, but individual cases of carcinoma occurring at an unusually early age are sometimes met with, as in one of the families mentioned above, in which the probable effect of heredity cannot be disregarded."

It seems, therefore, that the evidence both for the human subject and for breeding experiments on mice, points in the same direction. Heredity does have a slight influence, and occasionally may exercise a quite appreciable influence. Bashford and Murray,[1] however, issue an emphatic warning against alarm, by writing: "To guard against pessimistic conclusions it is well to point out that the influence of heredity has only been demonstrated by studying stocks in which this factor has been concentrated by careful mating, and that the influence is mainly exerted in the immediate descendants. Such a concentration as can be attained in experimental animals can only occur in the human subject by hazard, as a coincidence of considerable rarity, and it is probable that the influence of heredity in the general population is manifested as an average predisposition of low general intensity."

It is apparent that there are many difficulties in obtaining the facts upon which to base statistics of cancer, and that these difficulties are not all capable of being completely overcome even under the most favorable circumstances. The difficulties are greater in the country than in the towns, even in countries with the best developed statistics; they are still greater in the United States in general, owing to the vast distances, the numerous breaches of the registration laws, and the difficulty of obtaining correct records in small, isolated places. The immigration of from 900,000 to 1,000,000 persons annually, the floating character of this annual additional population, and of much else besides, greatly augment the difficulties of properly accounting for age and sex distribution. Moreover, the great inequalities in the education of those practising medicine in the United States militates against a general leveling up of the accuracy of the certification of causes of death. The falsification of the causes of death, in consequence of the physician's heeding the demand of the patient's family

[1] Introduction to the Fourth Scientific Report of the Imperial Cancer Research Fund, London, 1911.

that the return of the record of death shall not say cancer, is capable of being overcome to a large extent by making the record confidential and the intentional falsification of the death return a criminal offence both on the part of the doctor and on that of the persons instigating it. If the statistics of mortality are not to defraud the public which pays for such reports on the state bill of health, it is as essential to guard against the wilful suppression of a cause of death as it is to prevent the suppression of a birth, or the misstatement of the cause of a death really due to an illegal operation.

The difficulty of obtaining autopsies may be overcome by law, but is more likely to be overcome by educating the public concerning the value and harmlessness of the proceeding, and the fact that it is in their own interest. Autopsy is often refused, especially among some members of the Church of Rome, not from any doctrine of the Roman Catholic faith, but because many adherents of this church celebrate "wakes" over the dead body. For other reasons the poor hold to the sacredness of the dead body. For example, among certain foreigners in the lower parts of New York it is customary for the funeral cortege to proceed around the block before going to the cemetery, and thus to pass the tenement in which the deceased person had lived. Whether this custom be followed "for luck," for the deceased to have one last look, as it were, at the former place of abode, or out of respect to the dwelling place, it defeats the ends of science in many instances in which, otherwise, autopsy would be permitted, and in so far militates against the statistical study of the causes of death. All such practices and prejudices can be overcome only by education, just as objections to anatomical study have been overcome.

The greatest efforts are made to obtain accuracy of mortality statistics in England. For many years, whenever a death has been certified vaguely, the doctor has been written to, and exact information obtained. In this way, in 1911 alone, out of 12,563 such inquiries made, 10,718 replies were received. The data of the population, the numbers of the two sexes, the numbers living at each quinquennial age-group, and in town and country, are therefore ascertained with a fair approach to accuracy, although little account can be taken of the effect of emigration. Moreover, the deaths occurring in institutions are known and are transferred to the place of abode. As regards cancer, the individual sites are tabulated and a vague statement of death from cancer is inquired into and the site or organ ascertained. In this way, although the ideal has by no means been attained in that country, the statistics of death can have a larger number of "corrections" applied to them than anywhere else.

SUMMARY

The statistical study of cancer is valuable in many directions, both negative and positive—in other words, by what it proves cancer *is not,* as well as by what it proves cancer *is.* It has brought out marked differences between cancer and the epidemic or filth diseases; it has shown that all races and creeds are liable to the disease, irrespective of diet, soil, or climate, although the question of *relative* liability of different parts of the world and of different races has not been settled.

It has revealed the importance of chronic irritation by demonstrating how the distribution of cancer in the body may be altered by peculiar practices pertaining to native customs or occupations.

Statistics have revealed the relation between cancer and age —that it is rare under 35, but frequent after middle life—and that the relation of age ("age-incidence") differs for different organs, but is the same for the same organ in the two sexes.

Women suffer more from cancer solely because of the liability of the mamma and uterus to the disease. If these organs are deducted, the stomach and intestines are most liable in both sexes, although the male is more prone to attack, the indications being that alcohol and other irritants may determine his greater liability.

There has been a great increase in the *total* number of deaths recorded from cancer, partly due to improved certification of causes of death and improved diagnosis, and also because more people nowadays attain to ripe years. This must not be confounded with the question of a *relative increase.* When the figures are analyzed it is shown that there has been no relative increase for some parts of the body, for example, skin, uterus, ovary, liver, but that for other sites, notably stomach and intestines, breast and tongue, there has been a relative increase. The question whether this relative increase is real or only apparent has not yet been decided. There is some probability that a good deal of the increase for the stomach and intestines may be explained by improved diagnosis and certification of causes of death, owing to the improved methods of surgical diagnosis, but for the tongue and breast this would hardly hold. In the case of the breast, the increase in the inability of women to suckle their children calls for investigation.

Heredity has been shown to play a rôle, but not one to cause anxiety.

Finally, statistics have disposed of some popular fallacies regarding "cancer houses" and the risks of infection so widely feared.

SECTION IV

ETIOLOGY

CHAPTER I

THEORIES

EARLY THEORIES

DESPITE the seeming absurdity of such theories, Hippocrates, Celsus, and Galen conceived that there were four cardinal fluids in the body—blood, mucus, yellow bile, and black bile. An excessive accumulation of black bile was thought to be the cause of cancer, which term, for them, covered not only such of the true carcinomata and sarcomata as they had recognized, but much else besides. Their classification went little further than distinguishing malignant ulcers from malignant tumors, cancer *apertus* from cancer *occlusus*.

Early anatomists, like Vesalius, Fallopius, and Leonardo da Vinci, did much to break away from the domination of the humoral theories, which had held for centuries. Paracelsus made a further advance; and the treatment adopted by the famous surgeon, Ambroise Paré, shows that, like his predecessor, Leonidas, he had emancipated himself from the doctrine of Hippocrates, never to operate on an "open" cancer.

But, even at the end of the eighteenth century, famous anatomists, like John Hunter and Alexander Munro, still remained under the influence of the old humoral theories as modified by Descartes. The discharge of ulcerating cancer came to be widely designated as the "cancerous virus," and was regarded as its chief characteristic; so much so indeed, that, in 1773, a prize was awarded to the author of a famous book (Peyrilhe), describing how sloughing had been produced in a dog by subcutaneous injection of a discharge obtained from a man.

Walshe,[1] writing in 1846, said with reference to the various

[1] Walshe, Walter Hayle.—"The Nature and Treatment of Cancer," London, 1846, p. 35.

theories of the origin of "cancerous substance": "The majority of these are either so *prima facie* absurd, so insignificant, or so repugnant to the results of sound observation, that they are only fitted to figure among the curiosities of medical literature. The reader may well be spared an inquiry into speculations ascribing cancer to atrabilis or a melancholic humor—to lymph converted into an acrid and destructive fluid—to the presence of a gas possessing properties analogous to those of hydro-sulphuric acid—to fluids spontaneously effused and rendered corrosive by putrefaction—to the depravation of the nervous fluid—or to the presence and action of a virus composed of an ammoniacal fluid containing oxide of nitrogen in excess."

"With these vain hypotheses," quoting further from Walshe, "may assuredly be classed that which, under different forms, seeks to connect the appearance of cancer with the presence and agency of parasitic animals. I should indeed," he continues, "scarcely have conceived it necessary to advert more particularly to this theory than to the others, just mentioned, had it not been very recently revived with considerable pretension. It appears to have first attracted attention through the writings of Justamond,[1] an author of the last century, who ascribed the formation of cancer to 'insects, or the germina of these, taken up from the air by the lymphatic vessels.' He quotes a thesis by Martin Schumacher, and the work of Quadrio,[2] to show that he was by no means singular in entertaining this opinion. The latter writer had seen the insect, and described its length, breadth, and colour."

I have reverted to the opinion of Walshe, who was a distinguished member of the medical profession of his day, a careful observer, and a fluent writer, to show how, so far as the etiology of cancer is concerned, the past is linked with the present. The last influence of the old humoral conception of cancer did not disappear until the time of Virchow, or about the middle of the last century. The influence of the theories of the parasitic origin of the disease may be said to continue to be felt down to the present moment. Those who have followed the history of the modern study of cancer have been carried through a succession of hypotheses as to the causative influence of protozoa, entozoa, and various vegetable and animal parasites, some of which still figure in cancer literature.

[1] Justamond, J. O.—"An Account of the Methods Pursued in the Treatment of Cancerous and Scirrhous Disorders and Other Indurations," 1870, p. 65.

[2] Quadrio, Giuseppe Maria.—"Nuvo mètodo por curare ogni canchero coperto e specialmente le ghiande scirrhose delle mamelle, e di altre porti del corpo," Venezia, 1750.

THEORIES WHICH HAVE ENGAGED ATTENTION SINCE THE BEGINNING OF MODERN CANCER RESEARCH

BIOLOGICAL THEORIES

Influence of Humoral Theory upon the Scientific Study of Cancer.—Virchow, while forever liberating pathology as we know it to-day from the incubus of the humoral conceptions of disease, had not entirely rid himself of their influence when he considered tumors and cancer as crystallizing out of a universal connective tissue matrix. He showed his common sense, however, by not continuing his *Onkologie* [1] after the publication of the investigations of Thiersch [2] and Waldeyer,[3] whose demonstrations as to the histogenesis of cancer from corresponding tissues, entirely upset his ideas.

Yet how tenaciously the old humoral ideas of disease continued their hold upon the medical mind, and how widely they separate the standpoint of forty years ago from that of to-day, may be illustrated by the writings of the distinguished English surgeon and pathologist, Sir James Paget.[4] That he was familiar with the work of Virchow is evident from frequent references in his "Lectures on Surgical Pathology," published in 1853. Yet in 1874, in a debate at the Pathological Society of London, he still defended the views he had set forth in 1853 as to the humoral origin of cancer. As it is most important in the interest of medical education, alike of the profession itself, and of the laity, that there should be no misunderstanding as to what was known or debatable forty or fifty years ago, and what is no longer even debatable to-day, it seems advisable to give the following quotation from Paget's famous book. Writing of cancerous growths, he held that "They are local manifestations of certain specific morbid states of the blood; and that in them are incorporated peculiar morbid materials which accumulate in the blood, and which their growth may tend to increase."

"In the terms which are more usual in discussions respecting the nature of cancers, I would say that a cancer is, from the first, both a constitutional and a specific disease. I believe it

[1] Virchow, Rudolph.—"Die Krankhafte Geschwülste," 1863-65.

[2] Thiersch, Carl.—"Der Epithelialkrebs, namentlich der Haut," Leipzig, 1865.

[3] Waldeyer, W.—"Die Entwicklung der Carcinome," Virchow's Archiv, Vol. 41, 1867, p. 470. *Ibid.*, Vol. 55, 1872, p. 67.

[3] Paget, Sir James.—"Lectures on Surgical Pathology," London, 1853.

to be constitutional, in the sense of having its origin and chief support in the blood, by which the constitution of the whole body is maintained; and I believe it to be specific, first, in the sense of its being dependent on some specific material, which is different from all the natural constituents of the body, and different from all the materials formed in other processes of disease; and, secondly, in the sense of its presenting, in a large majority of cases, structures which are specific or peculiar both in their form and in their mode of life.

"The evidences of this hypothesis appear in the conformity of cancer to the other specific diseases, for which a similar hypothesis is nearly proved, and in the fitness of the terms which it supplies for the general pathology of cancer."

"The general history of cancers," he continues, "and their analogy with other diseases that are, in the same senses, specific and constitutional, imply that, before the formation of a cancerous growth, two things at least must co-exist; namely, a certain morbid material in the blood, and some part appropriate to be the seat of a growth incorporating that material, some place in which the morbid material may assume, or enter into, organic structure.

"The existence of the morbid material in the blood, whether in the rudimental or in the effective state, constitutes the general predisposition to cancer; it is that which is, by some, called the predisposing cause of cancer. The morbid material is the essential constituent of the 'cancerous diathesis, or constitution': and when its existence produces some manifest impairment of the general health, independently of the cancerous growth, it makes the 'primary cancerous cachexia.'

"That which evidently makes some part of the body appropriate for the growth of a cancerous tumour is a so-called exciting cause of cancer; but it is a cause of cancer only in so far as it fits some part of the local manifestation of a disease which already, in its essential material, exists in the blood.

"It seems very important to keep constantly in view that these two conditions must coincide before the appearance of a cancerous growth; important not only to recognize their existence, but, if we can, to measure the several degrees in which, in each case, they are present; because, upon our recognition of the shares in which they respectively contribute to the production of the cancerous tumour, must depend the chief principles of practice in relation to the removal of such tumours. The larger the share taken by the constitutional element of the disease,—that is, by the cancerous condition of the blood,—in the production of a cancerous growth, the less is the probability of advantage to be derived from the removal of that growth; while, on the other hand, the more largely the local state enters into the conditions upon which the cancerous growth is founded, the more benefit may we anticipate from the removal of the cancer and of the locality with it."

It is not surprising that Paget, holding such views, despaired of the treatment of cancer by surgical removal, as did Syme, Benjamin Brodie, and other distinguished surgeons of that time. As shown in the chapter on Histopathology (Section V, p. 142), such theories were then opposed only by Moore and De Morgan, who were ahead of their times in advocating views in accordance with modern conceptions of the circumscribed origin of cancer. To-day the old pathology of Paget is paraphrased and set forth as something new by certain self-styled "cancer-specialists" who do not scruple to use the name of Paget, Syme, Brodie, and others, to give the appearance of authority to their writings.

By 1887 the morbid condition in the blood had become a micro-organism for Paget. He then wrote:[1] "I think that we may justly hope to find a remedy in the constant and careful study of the likeness of these diseases to others of which we already have means of useful treatment. We may be the more hopeful because of the nearest likenesses of cancer and cancerous diseases are to two other groups of diseases, concerning which there have been in most recent times, very useful additions to our knowledge. In one direction we have their likeness to the simple or innocent tumours, in the surgical removal of which the risk of life has been diminished, even while the range of operating has been increased; and in the other direction we have their likeness, which I believe to be much more intimate, to some of the specific and micro-parasitic diseases, a group in which there has been progress toward both preventive and remedial treatment."

Paget developed his views along the lines that the dissemination of cancer was like that of pyemia rather than what would be expected if transported cells gave rise to emboli. In 1887 he still deplored the many failures of surgery, but nothing now justifies quoting him as an opponent of surgery even in those days of still unperfected technic and vague knowledge.

As has been described under structure, it is now known that cancer arises in a circumscribed area, and is derived from cells preëxisting in the part in which it arises, whether these cells be in their normal situation or displaced because of some ab-

[1] Paget, Sir James.—The Morton Lecture on Cancer and Cancerous Diseases. *Lancet,* November 19, 1887, p. 999.

normality of development. The problem of causation resolves itself into explaining the progressive growth of cells derived from corresponding cells of the organism itself, and behaving, anatomically and physiologically, quite independently of it.

Virchow's Theory.—Virchow[1] put forward the first rational theory of causation. As we have already seen, his idea that the cancer cells crystallized out of a connective tissue matrix was shown to be wrong, but his attribution of cancer to the effects of chronic irritation is still widely held to be correct. Virchow thought chronic irritation produced a granulation tissue which, like early embryonic tissue, was undifferentiated in appearance, and thereupon differentiation took place in the form of the tumour.

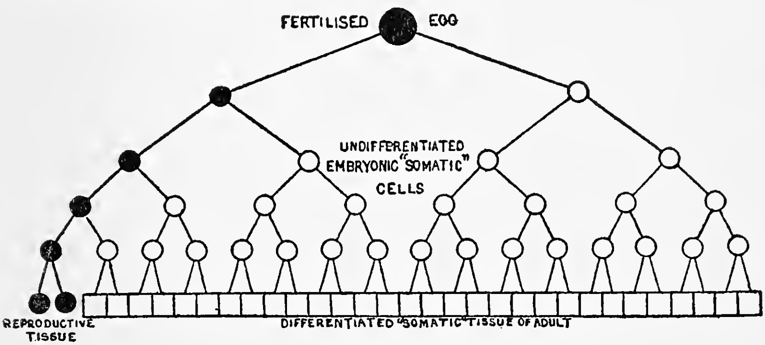

Fig. 1.—Diagrammatic representation of the differentiation of somatic and reproductive tissues in the higher animals, indicating the limitation of the amount of growth which determines the size of the body, and also the duration of life.

Thiersch's Theory.—Thiersch,[2] benefiting by the advance of embryological and histological study, was able to derive carcinoma of the skin from the skin itself, and sharply to differentiate the epithelium from the connective tissue. He sought the explanation in *a disturbance of the equilibrium established between epithelium and connective tissue.* According to him, with advancing age the connective tissue ceased to be able to hold the epithelium in check, and it therefore grew into the former. The modern conceptions of development and of the relations between cancer cells and the connective tissue are quite the opposite, viz., that the epithelium determines the character of the connective tissues during the development of the several organs, and that the cancer cells mold the con-

[1] Virchow, *op. cit.*
[2] Thiersch, *op. cit.*

nective tissue to their special requirements. Thiersch did not deny that chronic irritation, inflammation, or injury might be indirect causative factors.

Waldeyer's Theory.—Waldeyer,[1] following up Thiersch's work, came to the conclusion that all carcinomata were epithelial growths derived from the corresponding epithelium, and that the secondary growths were the offspring of transplanted cells, and not a transformation of the tissue in which they occurred. He drew a sharp distinction between carcinoma and sarcoma, and held that the latter was likewise a connective

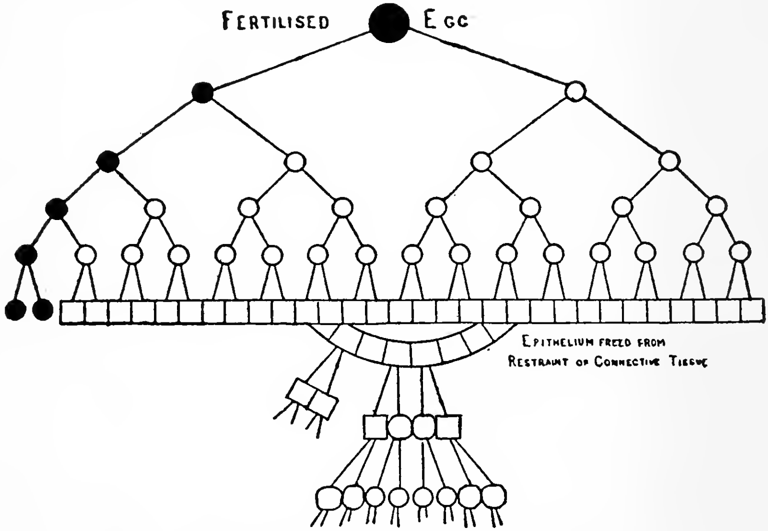

Fig. 2.—Diagram of the hypothesis of Thiersch and Waldeyer. The earlier senility of the connective tissues was assumed to allow of renewed, unlimited growth of epithelium. The cells were further assumed to revert to an embryonic type as represented in the last row.

tissue tumor. Waldeyer was impressed with the great vascularity of early malignant new growths, and with the accumulation of white blood corpuscles, so that the appearances were almost those of inflamed tissues. He asks, therefore: "Is it not possible that the excessive nourishment and loosening (*'Lockerung'*) of the connective tissues thereby involved, assist in the advance of the epithelial cells? Is it not possible that in this way local chronic inflammatory processes—especially those arising from repeated irritations which cause circumscribed inflammation—may eventually pass over into cancerous degeneration?" These questions, he held, deserved the most

[1] Waldeyer, *op. cit.*

earnest examination, as perhaps from them might be obtained some valuable indications for the prophylaxis of cancer, particularly as already a number of other experiences, especially those of a clinical nature, pointed to some connection between chronic inflammatory stimulation and cancerous degeneration.

Thus Waldeyer, while finally disposing of the actual descriptive basis of Virchow's views, and of those of all his predecessors, was also able to give a renewed lease of life to the importance which Virchow attached to chronic irritation. It will be noted that Waldeyer conceived repeated irritation to be the essential factor. He also entertained the probability that an entire organ was liable to cancer, and for this reason advised extensive operation.

Waldeyer differed from Thiersch in holding, that not the connective tissue, but the epithelium, became weakened with advancing years, and that the greater or increased activity of the connective tissue led to the epithelium being isolated and surrounded with sclerotic tissue, in consequence of which it might undergo cancerous transformation.

Cohnheim's Theory.—Cohnheim [1] elaborated a view originally expressed by Remak.[2] According to this theory, which was dominant for many years, cancer arose in persistent embryonic rests which, owing to their displacement from their normal environment, had not been incorporated during the normal development of the organism, and had not degenerated. Thus cancer was simply a renewal of embryonic growth, the potentiality for which, in consequence of the displacement, had been retained. The theory did not explain why these cells remained latent for years, nor why only an occasional "cell rest" developed into cancer. Subsidiary hypotheses were called in. Irritation was again called upon to explain why latent germs began to grow actively. The greater frequency of cancer at the openings of the body than throughout the length of the tubes; its greater frequency in parts where congenital displacements were more common or the processes of development more complicated, were alleged as evidence.

It would take too much space to put forward all the arguments for and against Cohnheim's theory. It may be stated, however, that tumors and malignant new growths do arise at times from what are the results of anomalies of development, for example, teratomata and mixed tumors. Nevertheless, the

[1] Cohnheim, Julius.—Vorlesungen über allgemeine Pathologie. Vols. 1 and 2, 2nd ed., Berlin, 1882.

[2] Remak, Robert.—"Ueber die Entwicklung der Geschwülste," *Deutsche Klinik,* 1854, No. 19.

superposition of malignant new growths upon the growth of embryonic tissue is to-day regarded as being just as much a problem for solution as is its acquirement by tissue still growing in normal continuity with its surroundings.

Ribbert's Theory.—Ribbert[1] further developed the idea of displacement of cells. According to his view, it was not so much development as post-natal displacement which was answerable for cancer. This theory has undergone so many modifications in order to meet criticism that it is not easily described. He held that displaced cells were without the

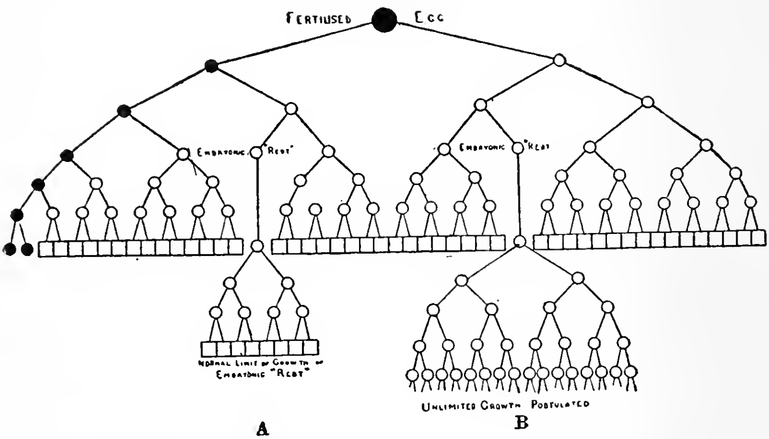

Fig. 3.—Diagram of Cohnheim's hypothesis. The different behavior of the progeny of "rest" A and "rest" B indicates the important assumption which the hypothesis entails. The necessity for this assumption was recognized by Cohnheim and deliberately made by him.

restraining influences of the body, and therefore simply gave expression to their natural powers of growth. Weigart had argued that there was no such thing as a stimulus to growth, and Ribbert accepted the view, maintaining that, in respect of their powers of growth, cancer cells had not departed from the normal.

It cannot be denied that, following injury and repair, as well as inflammatory conditions of all kinds, cells are often displaced and cut off from their normal connections. At the same time, the development of cancer is the exception and not the rule under these circumstances. Ribbert sought to show that very early growths were always sharply circumscribed and defined from the adjacent tissue, even from the corresponding

[1] Ribbert, Hugo.—"Geschwülste," Bonn, 1904.

epithelium. Against his studies, however, must be placed reliable observations which show that an early carcinoma may maintain continuity with the normal epithelium. Ribbert attached great significance to the occurrence of cellular infiltration in the connective tissue adjacent to early carcinomata, as being evidence that changes are taking place in the connective tissue, and that the epithelium never grows into unaltered connective tissue. The alteration in the connective tissue is affected by chemical substances proceeding from the epithelium. There are other subsidiary hypotheses, one of which is that the

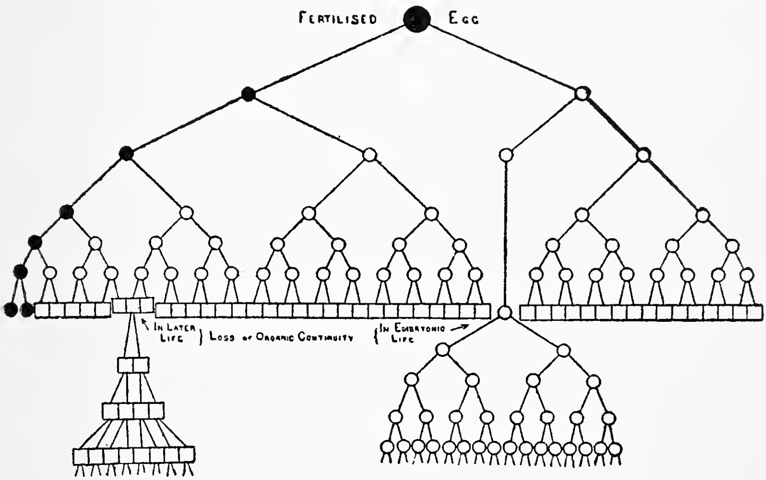

FIG. 4.—Diagram of Ribbert's hypothesis, showing the manner in which the differences in the degree of differentiation of different tumors was explained by him.

new connective-tissue environment effects secondary alterations, such as loss of differentiation, in the carcinoma cell.

The great value of Ribbert's theory lies in the stimulus given by it to the study of the earliest stages of cancer development, and in its revelation of the minute size of the area within which cancerous changes may be fully demonstrated, as opposed to the theory that an entire organ or tissue undergoes transformation. Thus, in great part, was built up the theory that cancer, once formed, grows from its own resources only, and not by accretion around the margins.

Hauser's Theory.—Hauser[1] put forward views almost categorically different. He postulated a fundamental biological

[1] Hauser, Gustav.—"Das Cylinderepithel. Carcinom des Magens und des Dickdarms," Jena, 1890.

difference between normal cells and cancer cells, the latter, in his opinion, being a "new race of cells," added to by the further production all round the margins of cells of the same kind. He reasoned by analogy with the variations in individuals and the production of species. He saw proofs of a biological change in the changed microscopical structure, in the alterations in the size of the cells, their nuclei and the chromatin, as well as in the increased power of multiplication.

Other Theories.—Adami, Benecke, Marchand, von Hansemann, and others, are responsible for a large group of theories which have something in common in that they seek to explain the power of growth in terms of loss of some other cell function; for example, differentiation and secretion, or injury to one part of the complex cell mechanism, permitting undue manifestation of what Adami calls the "habit of growth."

According to Adami,[1] a cell which has lost its differentiation, or which has never acquired it, continues to take up nourishment, passes into an active vegetative stage, and "gains the habit of growth."

Benecke [2] holds that the lowering of functional activity is accompanied by increase of growth energy.

Marchand [3] distinguished sharply between the undifferentiated embryonic cell and the undifferentiated tumor cell. The former, after continued growth, undergoes differentiation; in the latter the power of differentiation has not only become latent, but is permanently lost. There is some degeneration in the cell, leading to faulty metabolism, and the exercise of toxic action on neighboring cells weakens them and leads to their progressive growth.

Von Hansemann,[4] extending the work of Cornil,[5] Klebs,[6] and Podwyssozki [7] on cell division in cancer, described in detail the irregularities of cell division. He argued that these must result in changed biological characters, among others loss of function and differentiation, with acquirement of increased powers of growth. This alteration he names anaplasia, and asserts that it is not a theory of the origin of cancer, but only a description of actual findings.

Even more closely identified with changes in the nucleus are

[1] Adami, J. George.—"The Principles of Pathology," London, 1909.

[2] Benecke.—Ziegler's Beiträge zur path. Anat., 1892-1893.

[3] Marchand.—See General Bibliography.

[4] Von Hansemann, David.—"Studien über die Spezificität, den Altruismus und die Anaplasie der Zellen," Berlin, 1893.

[5] Cornil.—See General Bibliography.

[6] Klebs, E.—"Handbuch der pathologischen Anatomie," Berl., 1869. I, 307.

[7] Podwyssozki.—Ziegler's Beiträge zur path. Anat., 1886.

the views put forward by Farmer, Moore, and Walker,[1] that the cell divisions resemble those occurring in the ripening of the sexual cells. These views lack all independent confirmation, and Bashford and Murray[2] have shown the sources of fallacy underlying this interpretation of the chromatin figures in dividing cells. Oertel[3] has suggested that the nuclear chromatin is of two orders, one governing function, the other proliferation. By the loss of the former only the vegetative properties are transmitted to future cell generations.

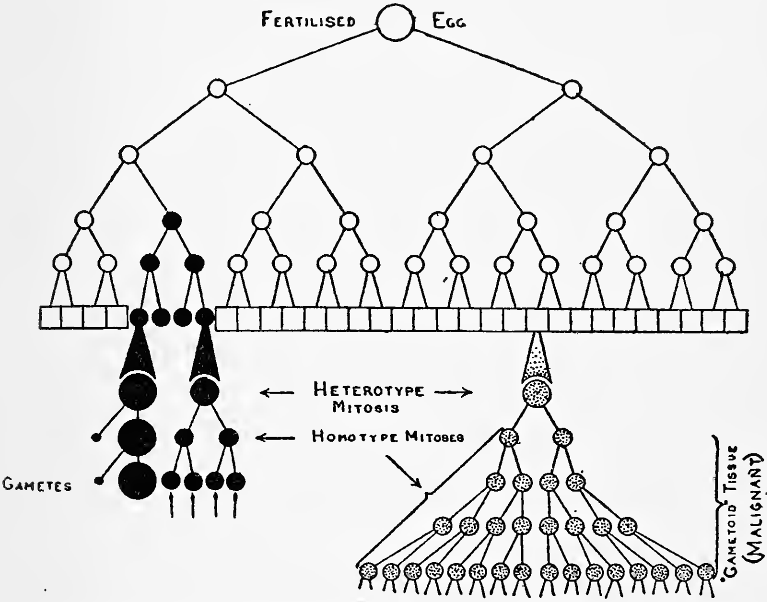

FIG. 5.—Hypothesis of "gametoid" nature of cancer (Farmer, Moore, and Walker). Cancer is assumed to arise from adult tissues in a manner analogous to that by which the normal reproductive tissues are separated from the soma in development. The properties and power of growth of cancer are regarded as analogous to those of reproductive tissue.

PARASITIC THEORIES

There remains for consideration the theory that cancer is caused by an external parasite. This view has long been held

[1] Farmer, Moore, and Walker.—"Resemblances Exhibited Between the Cells of Malignant Growths in Man and Those of Normal Reproductive Tissue," Proc. Roy. Soc., Vol. 72, 1903.

[2] Bashford and Murray.—"On the Occurrence of Heterotypical Mitoses in Cancer," Proc. Roy. Soc., B, Vol. 77, 1906.

[3] Oertel, Horst.—"On the Heterogenesis of Tumors, Particularly Cancer," *N. Y. Med. Jour.*, July 6, 1907.

in various forms, and a legion of parasites has been discovered. Not one of these has found any reasonable amount of support, and if cancer be communicated by such means, it may safely be said that the parasite still remains unknown.

The grounds on which cancer is held to-day to be infective are mainly statistical—the increase in the number of deaths from it recorded throughout the world, its alleged or apparent higher incidence in some districts than in others, and the alleged occurrence of "cancer houses." Alleged epidemics have

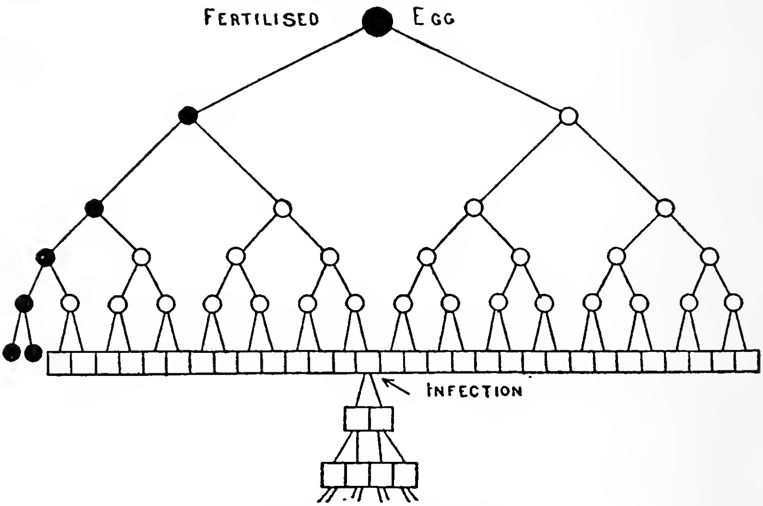

FIG. 6.—Parasitic hypothesis.
(The numerous assumptions entailed are discussed in the text.)

also been described in cows, rats, and fish. These have been dealt with in the section on Statistics.

It is also held that cancer is infectious because of a supposed resemblance to tuberculosis, but this view is based on a false analogy. In tuberculosis the tubercle bacillus is the cause of the disease, the bacillus itself being transported and spreading throughout the body, transforming its fresh nidus into the tuberculous process. In cancer, as is discussed under Histopathology, actual portions of the body grow in places where they should not be, having themselves been transported. Although the use of the term is hardly permissible, one part of the body has become parasitic on another part.

All the preceding theories may be placed in one or the other of two categories. It is assumed that an external stimulus of some kind causes growth, or it is assumed that some change taking place internally in the cell itself, permits of growth. The parasitic hypothesis is stated in both ways by its supporters. The alternatives have been succinctly expressed by Powell White,[1] who is not a supporter of the parasitic hypothesis:

"If the continued cell proliferation in tumours be the result of direct stimulation by an extrinsic irritant, such irritant must of necessity be a living organism, since the proliferation, being continuous and progressive, demands a continually increasing irritant. This applies equally to the histiomata and cytomata, and since, as we have seen, there is no sharp boundary between the two classes of tumours, we must infer that the essential causal factor is of the same nature in both cases. The supposed parasite must be either intra- or extracellular. If it is extracellular it is impossible to explain the absence of infection of the surrounding tissues; for, as we have seen, the growth of a tumour is the result of proliferation of its own cells, and the surrounding tissues take no part in it, except, in certain cases, in connection with the area of origin. . . . If, on the other hand, the parasite is supposed to be intracellular it would seem necessary to suppose that the division of the cell and of the parasite was so timed as to be simultaneous, each daughter cell receiving a daughter parasite. In all cases in which parasites are found within cells the effect is the destruction either of the parasite or of the cell.

"Since cell proliferation in tumours is similar to cell proliferation under normal conditions, the assumption of a parasite to explain it is quite unnecessary, and makes an explanation of tumour growth more difficult.

"Direct stimulation of cell growth by a parasite is an unknown occurrence in biology and is opposed to the facts of parasitism, and the difficulty is not avoided by applying, as some do, the term symbiosis as explaining the association between the supposed cancer parasite and the organism. In symbiosis the partners receive mutual benefit from the association, but symbiosis does not lead to proliferation.

"Numerous micro-organisms have been described by different observers as occurring in cancers, and for many years there has been a great controversy between those who uphold and those who deny that cancer owes its origin to one or more specific parasites. Investigation has been carried out both by histological and by cultural methods and, at different times, bacilli, cocci, torulæ, protozoa, myxomycetes, spirochætes, nem-

[1] White, Charles Powell.—"The Pathology of Growth. Tumours." London, 1913.

atode worms, and acari have been suspected as specific organisms for cancer, but no organism yet described has stood the test of criticism. No one has yet isolated from cancers any organism which will give rise to cancer when inoculated into other animals, except the cancer cell itself, which, as we have seen, will, under suitable conditions, continue to live and produce cancer when grafted into an animal of the same species as that from which the cancer was derived. Recent observations appear to show that it is possible to some extent for cells, both of normal tissues and of cancers, to proliferate *in vitro* as do bacteria. Undoubtedly bacteria and other organisms may be obtained from cancers, but their occurrence is apparently accidental, or at most incidental, as they do not stand in direct causal relationship with the cell proliferation." . . . "We have seen," he continues, "that we cannot ascribe the increased proliferative capacity of the cells to specific parasites, and it does not seem possible in any other way to explain tumour growth by the assumption of a specific causal parasite. It is impossible to account for the histiomata on this basis, and it is equally impossible to explain the complicated tumours such as blastocytomata, teratomata, and compound sarcomata. There only remain the sarcomata and carcinomata, and even in these cases the assumption of a specific parasitic origin leads to numerous difficulties. There are three possibilities to be considered.

"(a) There may be a single parasite for sarcoma and carcinoma. In this case it is impossible to explain the regularity with which metastatic tumours repeat the structure of the primary. We never find a primary carcinoma giving rise to secondary sarcomatous tumours as we should expect if both were due to the same causal parasite.

"(b) There may be one parasite for sarcoma and another for carcinoma. Here again the similarity of the metastatic tumours to the primary provides an insuperable difficulty. If all forms of carcinoma were due to a single parasite we should expect the metastases in the liver, in some cases at least, would show the type of hepatic carcinoma; this does not occur.

"(c) Each form of sarcoma and carcinoma may have its own specific parasite. Here we are at once met with the difficulty that the different forms of these tumours are almost innumerable, corresponding to the innumerable kinds of cells in the body. While they may be reduced to a limited number of type forms, yet there is no sharp boundary between the different groups, and there is considerable variation within the limits of each group. We should have to suppose a different set of cancer parasites for each organ, and not only this, but we should have to assume a different series of parasites for each species of animal! The fact that tumours are found in all genera of the higher animals, and have the same characters throughout, and yet it is impossible to graft a tumour from an animal of one species into another animal of a different species, while it is possible to do so within the same species, tells strongly against the theory of a parasitic origin.

"Other difficulties in the way of the parasitic theory are found in the close relationship of the cytomata to the histiomata and the relationship of tumours generally to malformations and to such conditions as progressive hypertrophy.

"We thus see that the assumption of a specific parasitic origin for cancer leads to insuperable difficulties in explaining the observed phenomena. These difficulties entirely disappear if we consider the cancer cell itself as a parasite and cancer as a process of infection by cancer cells."

SUMMARY

Naturally all older theories have been criticized in the light of the extensive experiments that have been performed since the beginning of the present century. For the most part the net result has been to show that all theories that yet have been advanced, constitutional, parasitic, or strictly cellular, are insufficient. The true, or even a satisfactory working explanation of the nature of cancer, has not yet been discovered.

CHAPTER II

PREDISPOSING CAUSES

With the inauguration, within the past fifteen years, of the era of experimental cancer research, efforts to solve the problem of the cause of cancer have assumed a character different from that of all previous investigation. None of the theories of the past concerning the essential cause having proved demonstrable, attention has now come to be more or less confined to the determination of the predisposing factors—with the hope that, in thus working out from indirect causes, the direct or essential cause may be discovered.

With this end in view, an enormous amount of experimental work has been done, and is now being carried on in the various research laboratories of the world, with reference to the influence of heredity, irritation, environment, diet, etc., upon the production of this disease. Of necessity the major proportion of these investigations has been made with short-lived animals, such as are available for laboratory use. Observations with respect to the various predisposing causes of cancer having a direct bearing upon the prevention and cure of the disease have been made, however, upon human subjects.

The Bearing of Experimental Investigation upon Existent Theories.—As explained in the section on Statistical Considerations, breeding experiments with mice have shown that a liability to cancer of the mamma may be inherited, but it is not settled whether this is a general constitutional liability or only a predisposition on the part of a single tissue. The balance of evidence favors the latter view. It has been made sufficiently evident that the effect of heredity is slight, and not of itself sufficient to explain the development of cancer.

The parasitic theory has received no support from experiment. Shortly after the transplantation of cancer in mice was demonstrated, von Leyden [1] expressed the view that this

[1] von Leyden, E.—"Ueber die parasitäre Theorie in der Aetiologie der Krebse," *Berl. klin. Woch.*, 1905.

achievement demonstrated that cancer is infectious. The opinion, however, was based upon a misconception of the process, and upon confounding infection with transplantation. By infection is understood the conversion of healthy tissue into cancerous tissue; transplantation, on the other hand, is the embedding of ready-made cancer cells into a healthy animal whose tissues no more become cancerous than does the soil change into geraniums when the latter are planted in it.

Borrel,[1] a firm upholder of the parasitic nature of cancer, has not used either his own or the transplantation experiments of others to support his view. He relies on apparent cage epidemics such as have been referred to elsewhere (see Section VI, p. 152).

Some authors have thought that the phenomena of immunity supported the parasitic theory, but the weight of authority goes to show that these phenomena have no analogy with what is established for infective diseases.

Recently Fibiger[2] has recorded that he was able to produce tumors of the stomach by feeding rats with cockroaches infected with nematodes. Out of several thousand rats experimented upon, true carcinomata developed in three. Some have thought the nematodes acted as the carriers of a virus in the way that Borrel first incriminated them for mouse tumors, because of the frequency with which he found nematodes in the lungs of that animal. Against this view it has been urged that the nematodes were not certainly shown to have caused the tumors, of which they may have been mere accompaniments, or alternatively, their causal relationship was merely that of any other chronic irritant.

The congenital or embryonic theory of the origin of cancer has received no support whatever from the experimental and comparative investigations of recent times. The production of cancer by irritants is determined solely by the point to which the irritant is applied, as by the Kangri in Kashmir, the chewing of betel nut in other parts of India, and the harnessing of a wagon to the right horn in cattle. To assume that congenital germs just happen to be present at the point where the irritant is applied is a needless assumption.

It must be remembered, of course, that cancer sometimes develops in a congenital anomaly, for example, in a teratoma; but

[1] Borrel, A.—"Le Problème du Cancer," Bull. de l'Inst. Pasteur, 1907, Vol. V, p. 497.

[2] Fibiger, J.—"Ueber eine durch Nematoden hervorgerufene papillomatöse u. carcinomatöse Geschwülstbildung im Magen der Ratte," *Berl. klin. Woch.*, 1913.

the explanation of the origin of cancer there is just as difficult as in the case of apparently normal adult tissues.

Experiment has shown that, after transplantation, tumors having no differentiation at all do not progress to differentiation as embryonic tissue does. Moreover, even when not differentiated the connective tissue or stroma usually has distinctive characters for different tumors. If cancer were merely undifferentiated tissue, one would expect the stroma always to show a uniform character.

On the constructive side, experiment, while revealing a very large number of new facts, has produced very little in the way of new theories.

Atreptic Theory (Ehrlich).—To explain his experimental results, Ehrlich has put forward the atreptic theory, which is a sort of mixture of a constitutional and a cellular theory. In it he seeks to explain the increasing frequency of cancer with age as the result of a lessening of the appetite for food on the part of the body as a whole, while certain cells retain their normal hunger, or at least lose less of it than does the rest of the body. Albrecht,[2] without performing any experiments, had previously put forward the view that the tumor cells acquired an increased avidity.

It must be remembered that Ehrlich's theory was advanced early in the development of recent experimental research, and therefore it is not surprising that the observations on which it is founded are not regarded as reliable by some other investigators. It is based on the following facts and conclusions: It is difficult to transfer a primary growth to new animals. The conclusion was therefore drawn that this was because the avidity of the bodies of normal animals was too high for the tumor cells. Ehrlich's transplanted tumors did not form any metastases, and he concluded that this was because the primary, transplanted tumor withdrew to itself all the food, thus starving the cells which were transported to the lungs. The same

[1] Ehrlich, P., and Apolant, H.—"Beobachtungen über maligne Maüsentumoren," *Berl. klin. Woch.*, July, 1905.

Ehrlich, P.—"Experimentelle Karzinomstudien an Maüsen," *Zeitschr. f. ärtztliche Fortbildung*, iii. Jahrgang, No. 7, April, 1906.

Also:

"Experimentelle Karzinomstudien an Maüsen," *Arbeiten aus dem Kgl. Institut f. exp. Therapie*, Heft I, 1906, pp. 77-102.

"Experimentelle Karzinomstudien an Maüsentumoren," *Zeitschr. f. Krebsforschung*, 1907, Bd. V, Hefte 1 and 2, pp. 59-80. *Abhandlung der Internationalen Konferenz für Krebsforschung*, Heidelberg, Sept. 25-27, 1906.

Ehrlich, P., and Apolant, H.—"Ueber die Genese des Carcinoms," *Verhandl. deutschen Path. Gesellsch.*, Zwölfte Tagung, Kiel, 1908.

[2] Albrecht, E. Rand.—"Bemerkung zur Geschwülstlehre," *Frankfurter Zeitschr. f. Pathologie*, Vol. I, 1907.

explanation was given as to why he could not reinoculate a mouse already bearing a tumor. Ehrlich also found that mouse tumors would grow for only a short time in rats, and he concluded that this was because the tumor cells were starved as soon as the foodstuffs introduced with them were used up.

All investigators are agreed on the difficulty of transferring a primary tumor from the animal in which it was produced to a normal animal, although the difficulty appears to vary with different investigators and with different methods employed. Bashford,[1] for example, found that young mice gave very much better results than did old mice, a fact now generally admitted by all workers, and which does not at all accord with Ehrlich's assumptions as to the part played by bodily avidity, because the contrary result should then be obtained.

Bashford and his colleagues have recorded a large number of other discoveries quite the opposite of those observed by Ehrlich. One of these is the fact that metastasis is frequent in their experience. They also explain Ehrlich's failure to reinoculate a mouse already bearing a transplanted tumor, as due to active immunity, which they claim to have fully demonstrated. The phenomenon of the transitory growth of mouse tumors in rats they explain as due to this active immunity, resulting from the formation of a true cytotoxin, such as is produced by the injection of the blood of one species into that of another.

Moreover, the demonstration by I. B. Murphy,[2] of the Rockefeller Institute, that mouse tumors may be kept growing through a long series of hen's eggs, nullifies entirely Ehrlich's opinion that, because of inability to assimilate foodstuffs specific to mice, mouse tumors grow only transitorily in rats.

The London school, consisting of Bashford, Murray, Haaland, Russell, and their colleagues, are apparently unwilling as yet to identify themselves with any particular theory or hypothesis, but full reference to their work is reserved for the section on Modern Cancer Research. At one time Bashford and Murray [3] confirmed certain findings by Farmer, Moore, and Walker,[4] to the effect that cancer cells had forms of cell-division similar to those characteristic of the ripening of sexual cells. They differed, however, from the conclusions drawn by

[1] Bashford, Murray, and Bowen.—"The Experimental Analysis of the Growth of Cancer," Proc. Roy. Soc., B, Vol. 78, 1906.

[2] Murphy, I. B.—"Transplantability of Tissues to the Embryo of Foreign Species," *Jour. of Exp. Med.*, 1913, p. 482.

[3] Bashford and Murray, *op. cit.* (p. 117).

[4] Farmer, Moore, and Walker, *op. cit.* (p. 117).

Farmer and his colleagues, and subsequently withdrew their confirmation of the findings of these investigators.

Chronic Irritation.—Although not openly expressed, the purpose which apparently lies at the basis of all the work of the Imperial Cancer Research Fund is an attempt to explain the association of many forms of cancer with chronic irritation. As the chronic irritants have nothing in common, it is held that there must be some properties in cells which are elicited by chronic irritation. Chronic irritation leads to prolonged or intermittent irritation, and for years, in propagating tumors, Bashford and his colleagues have demonstrated that many variations in structure and in powers of growth may take place. Just as what they describe as "new tumors" are produced during propagation by cell variation, so, they leave it to be inferred, by some such process, or a similar one, cancer is developed. It is not possible to define their position with any greater precision at present. (See Section VI,—Modern Cancer Research.)

Among the views recently expressed, mention must be made of the remarkable statement of Lazarus-Barlow,[1] who claims to have demonstrated that radium is present in larger quantities in cancer than in normal tissues; also that many of the irritants associated with cancer, like the clay pipe, or gallstones, are radioactive. These views are based on highly technical experiments and require confirmation.

Opinions differ as to how chronic irritation is related to cancer, some holding that it merely serves to make an entrance for a ubiquitous cancer parasite, others that the prolonged cell proliferation leads to cell variation. Notwithstanding such divergent points of view as regards etiology, one of the most clearly established facts about cancer is its production in tissues which have suffered chronic irritation, often of long duration. This association is naturally most often observed on the surfaces of the body; for example, on the skin and mucous membranes. The irritants are manifold—chemical, mechanical, actinic, bacterial, etc. One of the most striking instances is that of the development of cancer in a tongue attacked by leukoplakia. The well-known prevalence of cancer of the scrotum in chimney-sweeps is due in some way to soot; as paraffin, tar (Plate III), and arsenic are causative factors in other cases.

[1] Lazarus-Barlow, W. S.—"On the Presence of Radium in Some Carcinomatous Tumours and Other Tissues," Arch. of the Middlesex Hosp., Vol. XXVII, 1912. "On the Presence of Radium in Some Gall-stones and on a Correlation of This with the Frequency of Gall-stone Occurrence in Carcinoma," *Ibid.*

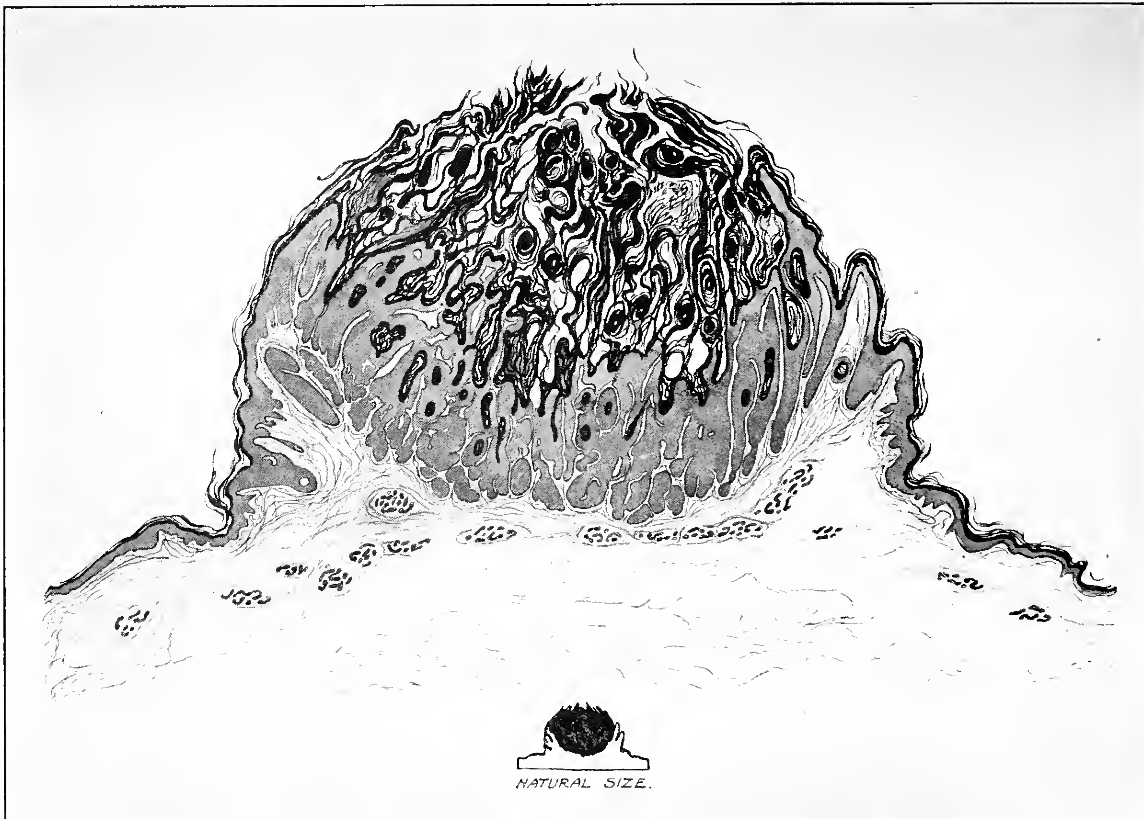

PLATE III.—Epithelial wart from the back of the wrist of a worker in shale (paraffin distillation). Such warts give rise to the skin cancers common in workers in paraffin, pitch, some forms of tar, and to chimney-sweeps' cancer. Also shows natural size.

In all these cases there has been long-standing dermatitis on which warty growths appear. In the bladder, cancer becomes superadded to the papillomata which develop in anilin workers or in bilharziosis. Chronic ulcers, sinuses, and even old scars from burns may undergo cancerous changes.

On the surface of the body it may not be difficult to determine that there has been chronic irritation, but with the internal organs, of course, such a cause is far more difficult to establish. For the stomach, opinion is divided as to the etiological significance of chronic ulcer; for the biliary and urinary passages, the same is true with reference to gall-stones and urinary calculi. In the case of the uterus, previous chronic metritis, or fissures of the cervix, have long been present. In the breast, however, chronic mastitis may never have been detected, and cancer of the breast may develop when it has never occurred. Certain pigmented moles may take on a malignant character either in consequence, or without the intervention, of irritation. In certain instances, as when cancer develops in a teratoma or sarcoma in the retina, it is very difficult to determine the part played by chronic irritation. Simple injury, such as a blow on the breast, or a fracture, may be followed by a new growth; but in these cases it is not always easy to determine whether the trauma simply draws attention to an already existing growth, or whether it exercises a causative influence.

I have repeatedly called attention to the importance of removing elevated nevi, papillomata, adenomata, and other benign growths which are subject to chronic irritation.

Precancerous Conditions.—It has long been customary to use the term "precancerous" with reference to certain conditions, notably glossitis and dermatitis, on which cancer supervenes. In Section V (Histopathology), p. 133, Butlin's experience with such supposed precancerous conditions of the tongue is related. It will be seen that five out of seven cases were proved to be early carcinomata. Therefore it has seemed to the author that the use of this term involves the danger that patients or their professional advisers may be encouraged to wait until cancer has developed before seeking surgical assistance, and that conditions which are of the nature of chronic inflammatory processes predisposing to cancer should be carefully watched, and any minute area which shows the changes which Butlin in his earlier experience would have called "precancerous" should be treated as if it were already cancerous.

Environment.—It is difficult to come to any conclusion regarding the etiological influence of environment. The effect of overcrowding has been considered in the sections on General Distribution and Statistics (Chapters II and III). The different liability of races living in widely separate parts of the globe cannot be determined. Soil, especially chalk, is held by some authors, whose statistics are called in question by others, to be important in increasing the frequency of cancer. It is said that cancer is more common in river beds than on elevated areas; more common where trees grow than where they are absent. It is held to be more frequent in the central plateau of Europe than elsewhere. But all these statements are of the nature of hearsay, and no reliance may be placed upon them.

The one form of environment, however, which does seem of importance in connection with cancer incidence is occupation. The liability of different parts of the body to develop either precancerous or cancerous conditions, in consequence of exposure to chronic irritation in connection with certain occupations, is fairly well established. Workers in tar, soot, petroleum, and anilin furnish illustrations of this contention. This is so well recognized that, in England, those trades in connection with which warty growths or cancer develop are scheduled as coming under the Workmen's Compensation Act. In some instances it is not the occupation so much as the liability to alcoholism that is held to be responsible for the development of cancer.

Diet.—The question of diet has given rise to a great deal of discussion, mostly taken part in by extremists. Hardly an article of food has escaped condemnation. Salt, tomatoes, coffee, meat—especially frozen or chilled meat—pork, and alcohol, all come under the ban. But the possible influence of diet is shown not to be very great by the liability to cancer of vegetarian castes in India, and of the rice, or rice and fish-eating Japanese. Cows never eat meat, and although both tame and wild mice are occasionally cannibalistic in their habits, they do not come in contact with pork, tomatoes, or alcohol. Neither do cows or other herbivorous animals liable to cancer eat their vegetable food cooked. Therefore, it seems that such sweeping views on diet as are published from time to time in lay papers are calculated to do a lot of harm.

SUMMARY

While the modern experimental investigation of cancer has thrown considerable light upon certain predisposing factors in the production of cancer, the essential cause is yet to be discovered. Perhaps the most practical outcome of such study is the emphasis to be placed upon the removal of all possible sources of chronic irritation, and of benign neoplasms which are subjected to irritation.

SECTION V

HISTOPATHOLOGY[1]

DEFINITION

The difficulty of considering cancer apart from tumors in general is as great with regard to questions of classification and structure as it is when considering the disease from the clinical point of view. It is apparent, of course, that all tumors or swellings are not malignant new growths; it is equally evident that malignant new growths—cancer—may be present when no swelling, but rather an actual loss of tissue, exists. Examples of the latter are seen in the shrinkage which occurs in scirrhus of the breast; in ulcer formation, as in squamous-cell carcinoma of the tongue; and in rodent ulcer of the skin.

These circumstances explain the difficulty of defining cancer, as they do that of defining tumors in general, particularly because the causation of both is unknown, and because all attempts at a sharp separation of benign from malignant new growths, or of either from tumors in general, meet with insurmountable difficulties.

Mere hypertrophy, or overgrowth, and inflammatory swellings, offer greater difficulties, as a rule, than do abscesses or cysts, although the latter, in certain instances, are not so easy of differentiation as abscesses, and may be malignant in nature. The difficulties are further enhanced by the fact that hypertrophy or chronic inflammation may precede or exist alongside of cancer, which may be superimposed upon such conditions.

In general, hypertrophy is diffuse, and the normal arrangement is maintained; whereas a tumor, especially a malignant

[1] The literature of histological investigation cannot be cited in a book of this scope without serious injustices and without calling forth serious criticism. A very full literature is given in the works of Borst ("Die Lehre von dem Geschwülsten mit einem mikroskopischen Atlas." Two volumes, Wiesbaden, 1902), and of Ribbert ("Geschwülstlehre für Aerzte und Studirende," Bonn, 1904. "Das Karzinom des Menschen, sein Bau, sein Wachstum, sein Entstehung," Bonn, 1911), to which the reader is referred.

new growth, is localized in one part of an organ whose normal form is disturbed thereby. Acute inflammation, when accompanied by a swelling, also exhibits other clinical features, such as rise of temperature, pain, etc., different from those present in the case of a true, uncomplicated tumor or a cancer. Chronic inflammation, however, owing to the formation of granuloma, such as one sees in syphilis, tuberculosis, or actinomycosis, may be associated with a localized increase in size. Such tumors often present great difficulty of diagnosis, more especially because the process of chronic inflammation leading to the formation of granuloma may pass on to true malignant growth, although, as a rule, with the removal of the cause such granuloma formations cease to increase in size and become absorbed.

As a general rule tumors grow progressively, although this is not universally the case. Some cartilaginous tumors, for example, found at the ends of the long bones, grow only during the period of development of the bones.

It will thus be seen that it is difficult to define a true tumor and quite impossible at present to give an exact definition of cancer. Adami[1] selects Powell White's[2] definition: "A tumour proper is a mass of cells, tissues, or organs resembling those normally present, but arranged atypically. It grows at the expense of the organism without at the same time subserving any useful function." Malignant tumors, in addition, usually exhibit active proliferation; they are not surrounded by a capsule, but fade off diffusely into surrounding tissues by virtue of their property of infiltrative growth; and they form fresh centers of growth at a distance, owing to the dissemination of cells by the lymph or blood stream.

When the normal structure is perfectly reproduced, or if it is sharply separated from surrounding tissues by a capsule, the tumor is said to be benign or innocent. When the structure is entirely lost and only a mass of undifferentiated cells is to be seen, it is said to be histologically malignant. It must be distinctly understood that these are merely terms of convenience, and that the biological properties of the tumor determine whether it is *clinically* malignant or benign. Some tumors, for example, the thyroid, are highly malignant and yet reproduce the normal structure perfectly. There are all grades between total loss and complete retention of structure.

[1] Adami, J. George.—"The Principles of Pathology." Two volumes. London, 1909.

[2] White, C. Powell.—"The Pathology of Growth—Tumours." London, 1913.

Practically all the cells and tissues of the body, with the probable exception of nerve cells,[1] are liable to tumor formation and to the development of malignant new growths. The term carcinoma is applied if the malignant growth be of epithelial origin, sarcoma if it be of connective-tissue origin.

The essential feature of cancer, whether it develops in a solid organ like the mamma, or on the covering surface of the skin of a hollow organ, is the continuous proliferation of cells. Since the process is practically the same for all. it is unnecessary to describe it in detail for each tissue.

VALUE OF HISTOLOGICAL STUDY

Many volumes have been written upon the minute anatomy or histology of cancer, often with the idea of setting up theories as to causation. The monumental work of Borst,[2] extending to 998 pages of print and 293 colored illustrations, and that of Ribbert,[3] amounting to 662 pages and 596 figures, may serve to show the magnitude of a subject which may be only briefly surveyed here. It is intended to convey merely the essential anatomical and microscopical features of the disease; to demonstrate its relation to normal tissues, in many cases its origin from them; its mode of growth, and the manner of its dissemination throughout the body.

The microscopical study of tumors, of their relations to surrounding textures, and of the spread of such of them as are malignant in character, has had a profound influence on conceptions of the nature of cancer, its origin, and its treatment.

It should be more fully recognized that this microscopic

[1] The thyroid gland illustrates this difficulty for epithelial tissues, but the development of secondary growths assists in arriving at a definite conclusion, which is not possible in the case of another class of tumors—in those developing in the central nervous system. These tumors, known as glioma or as gliosarcoma, are still of uncertain origin. Some, by growing progressively, produce a tumor whose effects may be described as those of mechanical pressure. Others grow in a diffuse and infiltrative way and not only involve the membranes of the brain, but may even penetrate the skull. Under the microscope these gliomata or gliosarcomata have the appearance of what is held to be the connective tissue of true nerve cells, but there is still discussion as to whether the normal gland is an epithelial or a connective tissue. In the retina so-called gliosarcomata also develop, but in that case it appears not to be doubtful that they are really carcinomata.

[2] Borst, Max.—''Die Lehre von dem Geschwülsten mit einem mikroskopischen Atlas.'' Two volumes. Wiesbaden, 1902.

[3] Ribbert, Hugo.—''Geschwülstlehre für Aerzte und Studirende,'' Bonn, 1904. ''Das Karzinom des Menschen, sein Bau, sein Wachstum, sein Entstehung,'' Bonn, 1911.

study is a modern method of investigation, which has proceeded in part along with, and in part subsequently to, the employment of anesthetics and antiseptics in surgery; and that, together with them, histology has placed a wide gulf between the surgery of cancer of thirty years ago and surgery as it is practiced to-day. That the influence of the study of the minute anatomy of new growths is still spreading is shown by the following quotation from the late Sir Henry Butlin,[1] who did so much to place the surgery of cancer of the tongue upon a scientific basis:

"I have frequently been greatly distressed at the long time during which actual cancer of the tongue has been under observation before either the medical man or the patient has become aware of the gravity of the disease. But I never knew until two years ago that I was myself guilty of failure to recognize cancer of the tongue in its earlier, if not its earliest, stages. And I might have remained in the same condition of ignorance had it not been for the work of the Imperial Cancer Research and the assistance of Dr. Bashford and his colleague, Dr. Murray, who have been associated with me throughout the investigation on which this paper is based, and to whom I am more indebted than I can tell.

"About two years ago Dr. Bashford asked me whether I could furnish him with very early conditions of cancer of the tongue for the Imperial Cancer Research. I replied that I would certainly do so, and that if I could I would do more than this, for I would furnish him with specimens of precancerous conditions of the tongue, so that he might study the transition into actual cancer. . . .

"Two years ago, before my eyes were opened by the work of the Imperial Cancer Research, I should have regarded five out of the seven as precancerous conditions, and I am now wondering whether there are really any conditions perceptible to human sight and feel which are precancerous in the sense in which I have been accustomed to employ the term.

"Many persons will wonder why I have been so slow to discover the true nature of these conditions. I can only answer that I am humiliated at my ignorance, and can only plead, in excuse for it, that I could scarcely ever, a few years ago, persuade patients to submit to operation for these conditions. And, if I had removed them, it is quite possible that their real nature might have been overlooked unless they had been exam-

[1] Butlin, Sir Henry.—"Illustrations of Very Early Conditions of Cancer of the Tongue," *Brit. Med. Jour.*, May 26, 1906. (With colored plate of clinical appearances and histological illustrations.)

ined in continuous sections after the manner which is now commonly practised in the investigations of cancerous and doubtful growths."

These conclusions of Sir Henry Butlin were accepted by another distinguished surgeon to whom he showed the microscopical preparations. In view of their far-reaching importance I thought it necessary to inform myself of the exact nature of the lesions upon which they were based. Owing to the lamented death of Butlin, application was made to Bashford, who had prepared a series of sections from which the drawings of an early cancerous ulcer of the tongue (Plate IV) were made.

HISTOLOGICAL APPEARANCES

The microscopical appearances of a tumor differ according to the degree with which the normal structure is reproduced or is departed from. When the tendency is to reproduction of the normal structure, as in the mamma, the cancer cells are arranged in groups somewhat after the manner of a bunch of grapes, but this characteristic of the normal mammary epithelium is not perfectly reproduced. The structure is easily recognized as not being typical of the gland, and varies from one area to another, so that the irregularity of the arrangement dominates the picture.

In transverse sections the natural gland spaces or lumina are imperfectly reproduced and are often of irregular shapes. Instead of being of uniform size they may show wide differences in this respect. The lumen of the normal gland may not be developed at all, and in its place only a solid mass of cells may exist. The walls of the lumina are formed, not by a single layer of cells, but by two, three, or more layers. When cut lengthwise the glandular tubules present similar irregularities in arrangement and size. Their branchings and their connections one with another depart widely from the normal, and often appear as if determined by spaces in the connective tissue in which they are embedded. The masses of cancer cells may be very minute or they may form relatively large masses connected by all imaginable branchings. The cells may be closely pressed together in solid masses, or they may be arranged in a single layer closely approximating to that of the normal gland, and all intermediate arrangements may be observed. The cells themselves, instead of being uniform in size, may vary greatly in their dimensions, generally tending to be larger than normal.

When the tendency is toward an entire loss of structure, the

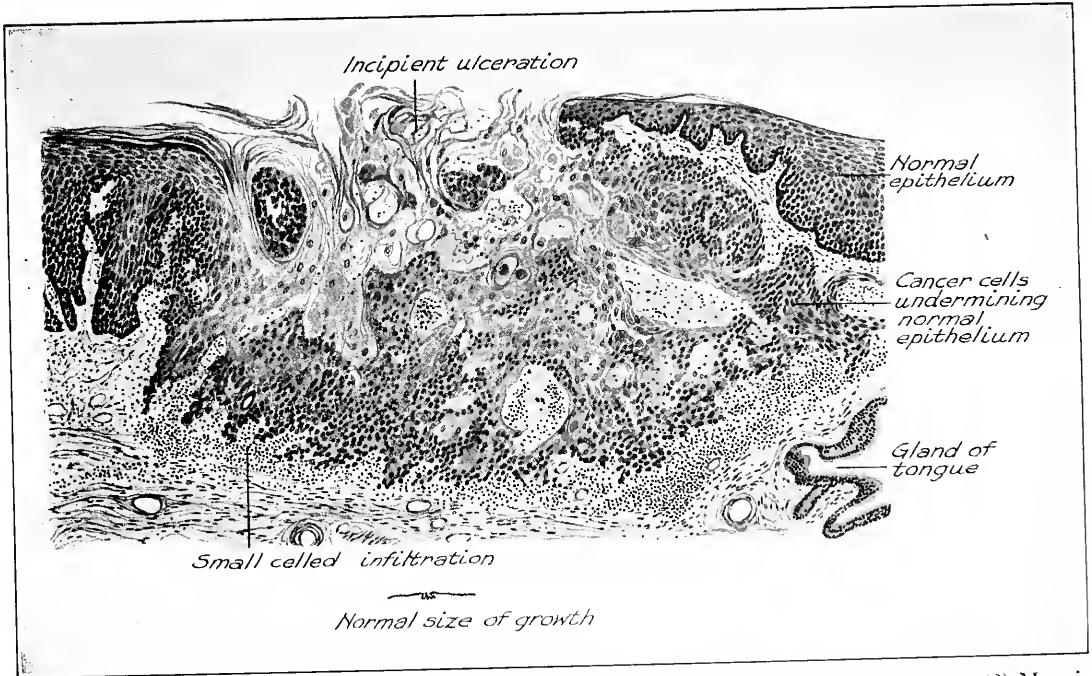

Plate IV.—(1) Natural size of an early squamous-celled carcinoma (epithelioma) of the tongue. (2) Magnified 50 times to show all the features of a small but fully developed carcinoma.

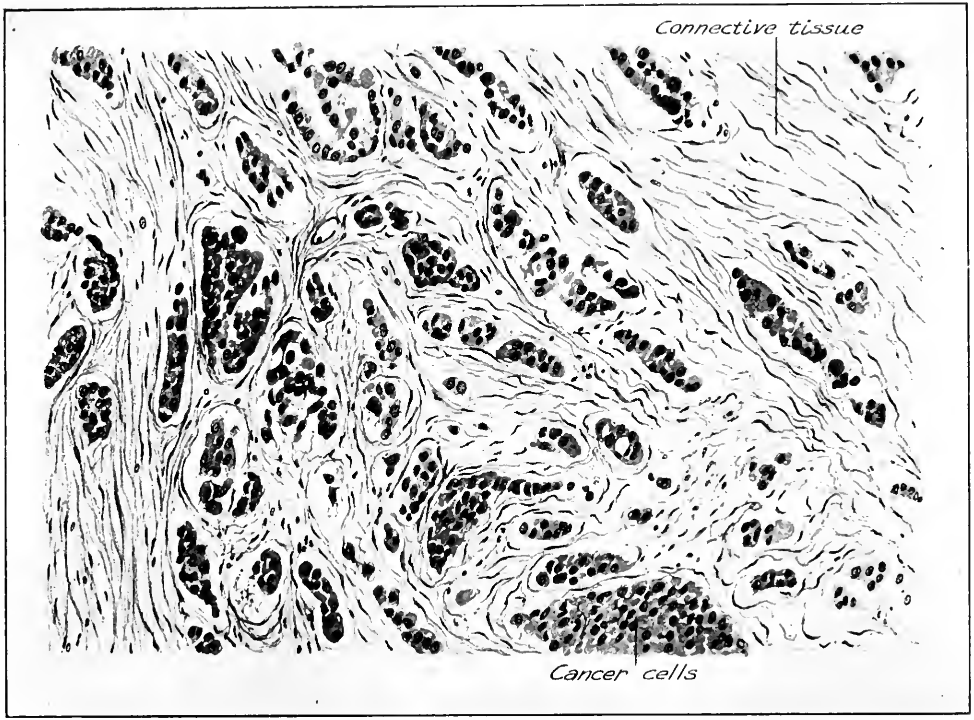

Plate V.—Carcinoma (scirrhus) of breast. Note solid strands of cancer cells growing in a very dense and abundant connective tissue.

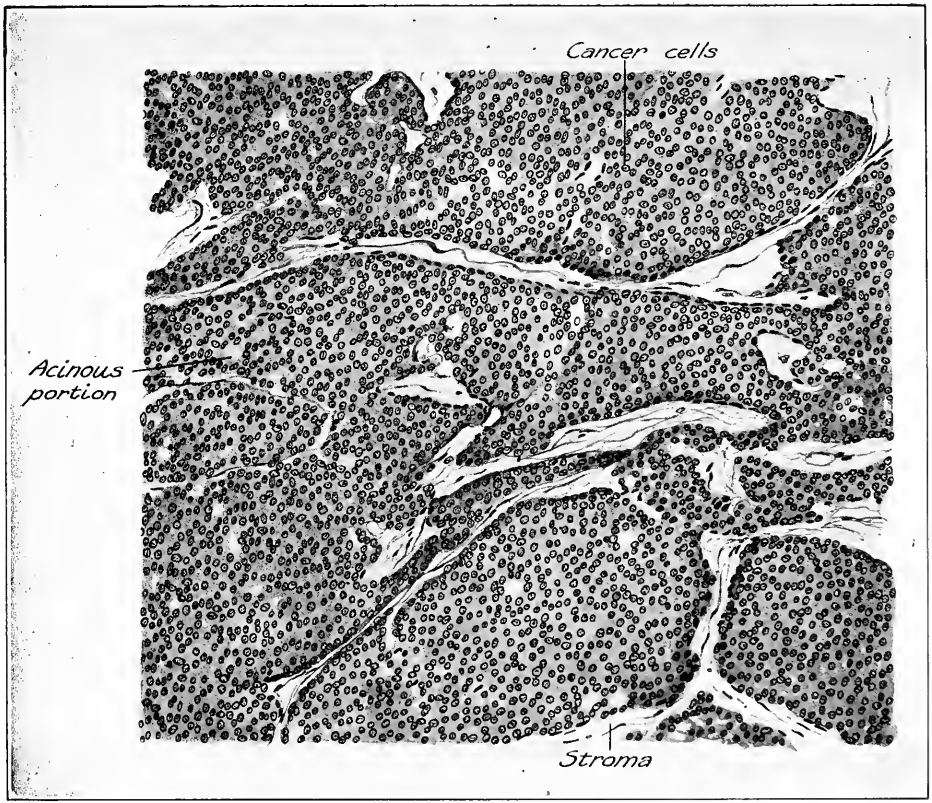

PLATE VI.—Soft or medullary carcinoma of the breast. Note very cellular nature and scanty stroma. There is a slight tendency to acinous or glandular structure.

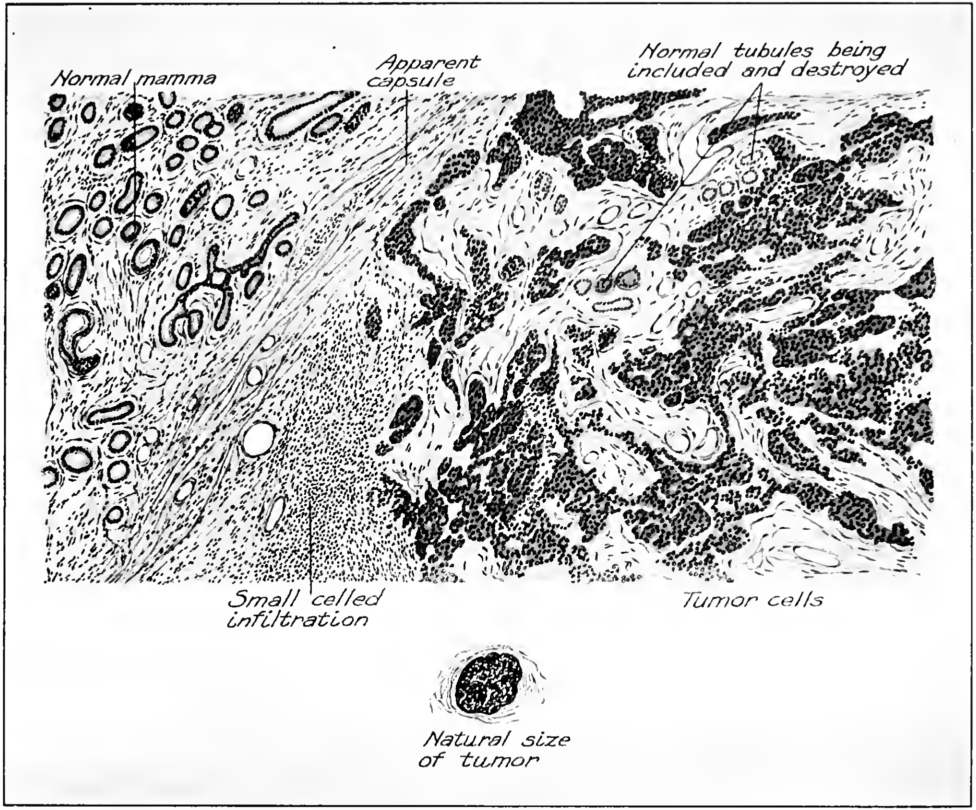

Plate VII.—(1) Natural size after fixation of a small carcinoma of breast for which whole organ was removed. The nodule lost about ⅓ in its size in the course of histological preparation. (2) Section through margin of nodule to show how the mammary tissue is being invaded and destroyed.

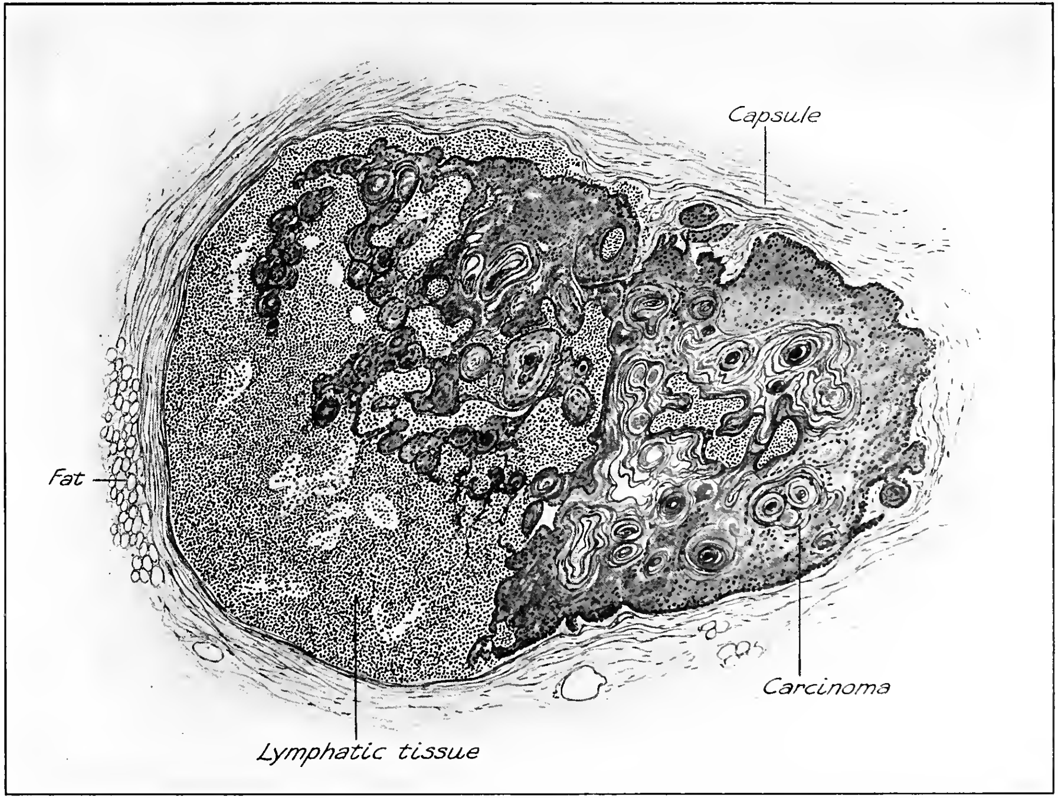

Plate VIII.—Squamous-celled carcinoma (epithelioma) growing in lymph gland which it has reached by way of the lymphatics entering marginal lymph sinus.

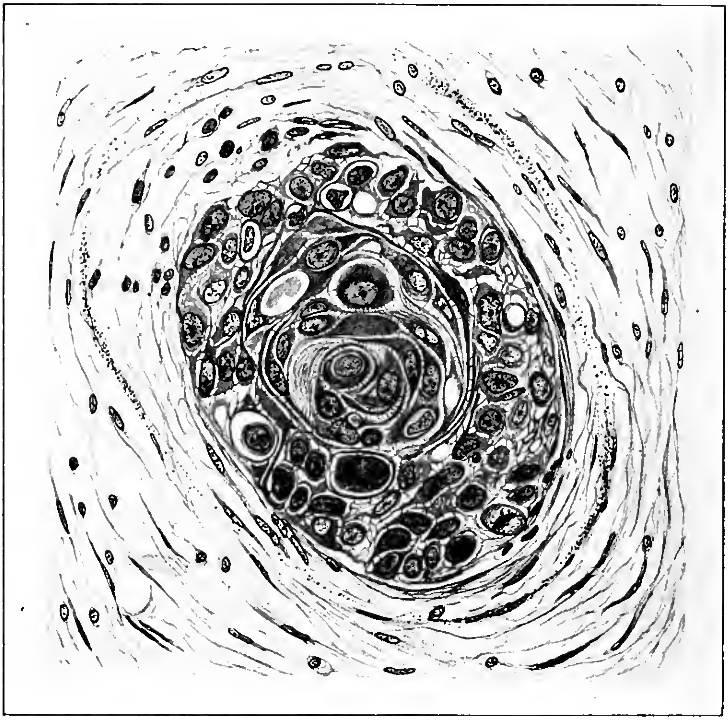

Plate IX.—Squamous-celled carcinoma (epithelioma) spreading by permeation of a lymphatic vessel, of which the lining endothelium is still partly retained.

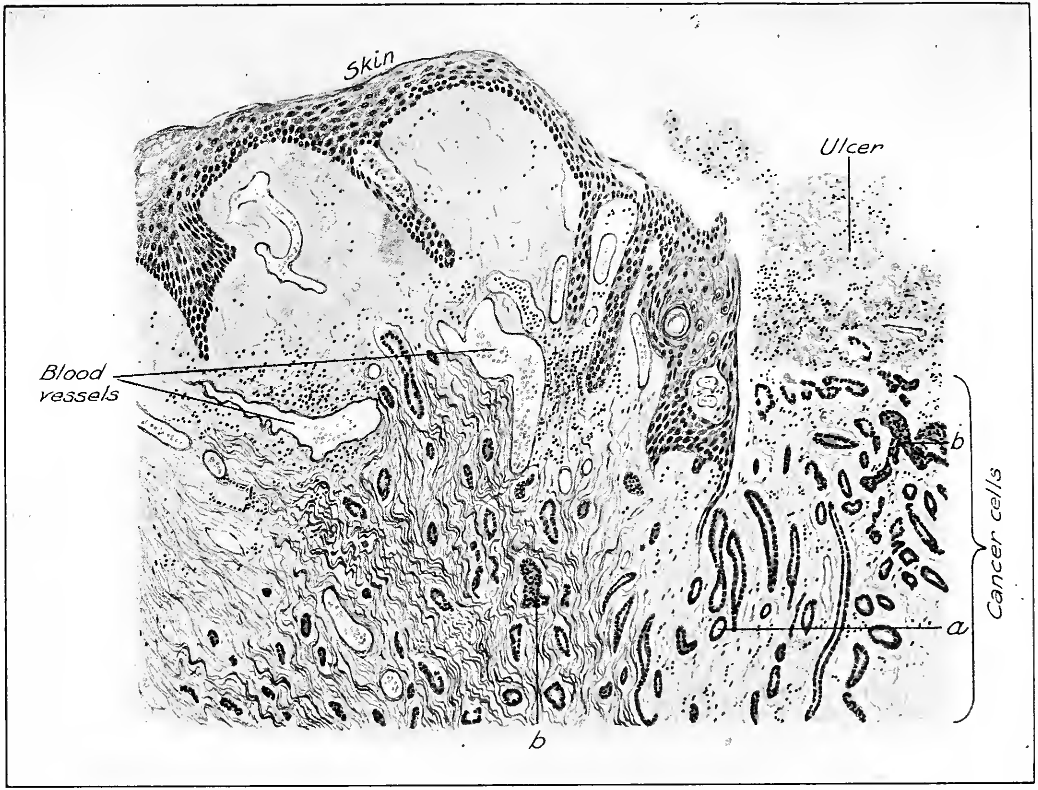

Plate X.—Ulcerating adeno-carcinoma of breast. The skin is being undermined and exfoliated by the tumor cells which in part (a) are reproducing perfectly the glandular structure of mamma in part (b) growing as solid cords. Note dense connective tissue.

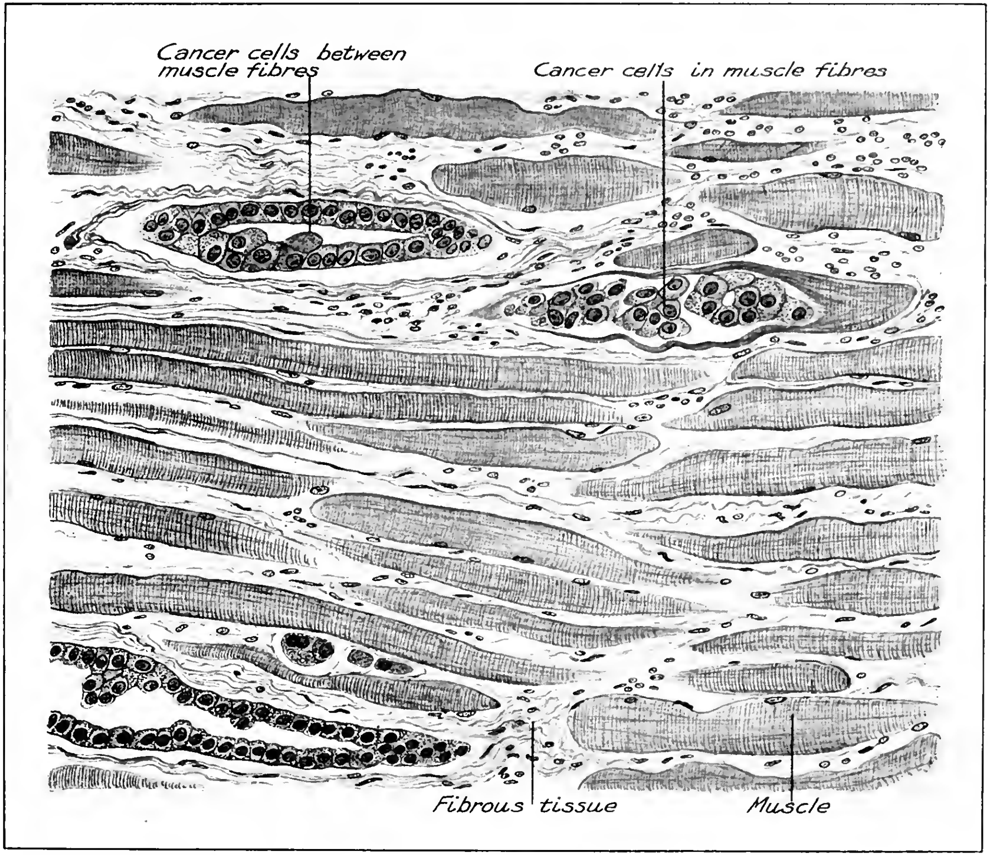

PLATE XI.—Spread of adeno-carcinoma of the breast between and inside muscle fibres of pectoral muscles.

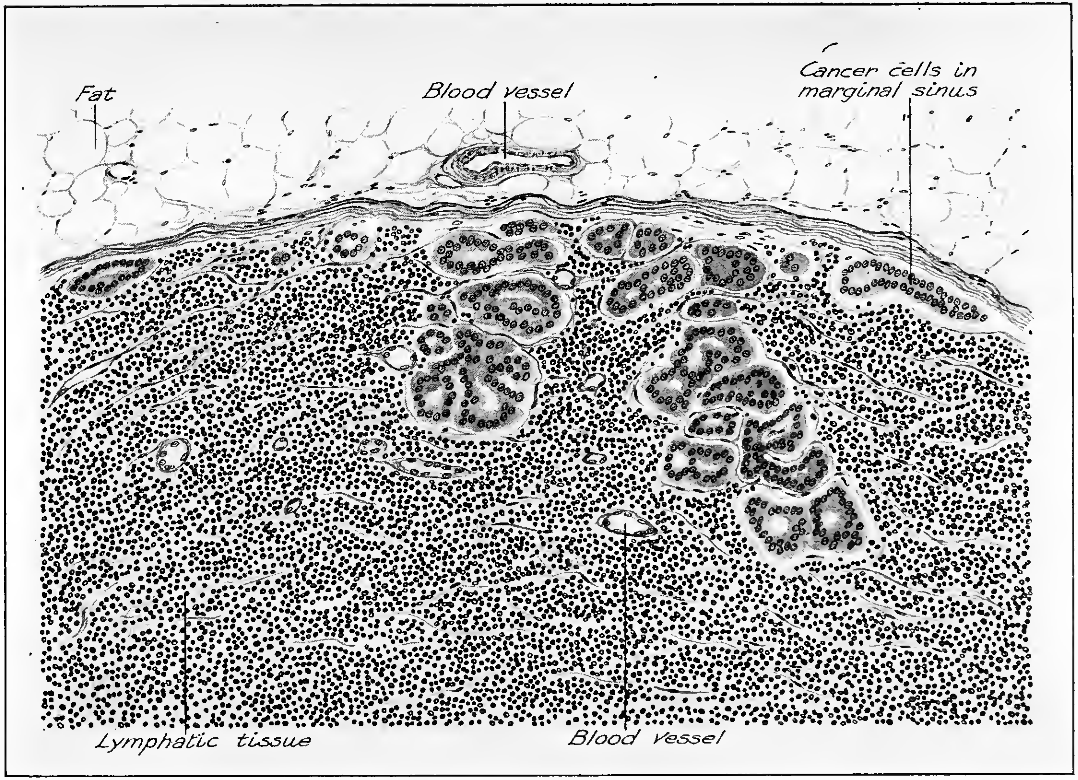

Plate XII.—Adeno-carcinoma of breast growing in a lymphatic gland which it has reached by way of the marginal lymph sinus.

PLATE XIII.—Invasion of a long bone by adeno-carcinoma of the breast.

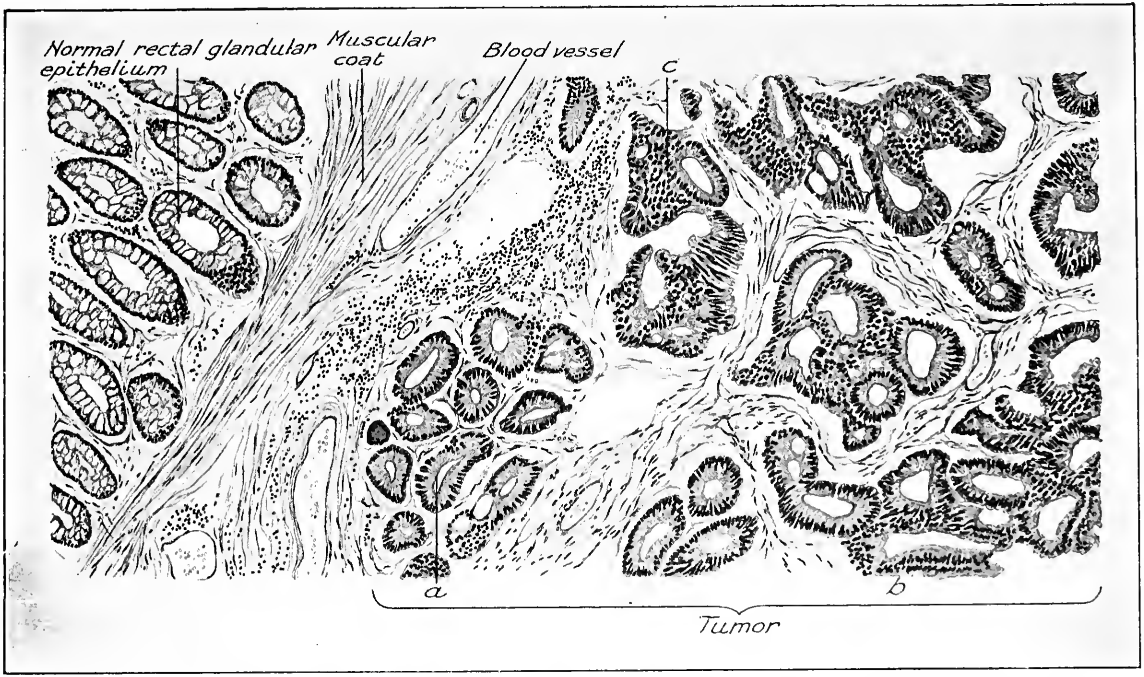

Plate XIV.—Adeno-carcinoma of rectum which has penetrated through the muscular coat and is growing on the peritoneal surface. Note at (a) perfect reproduction of glandular structure, and at (b) and (c) marked departure from it. Note richness in blood-vessels.

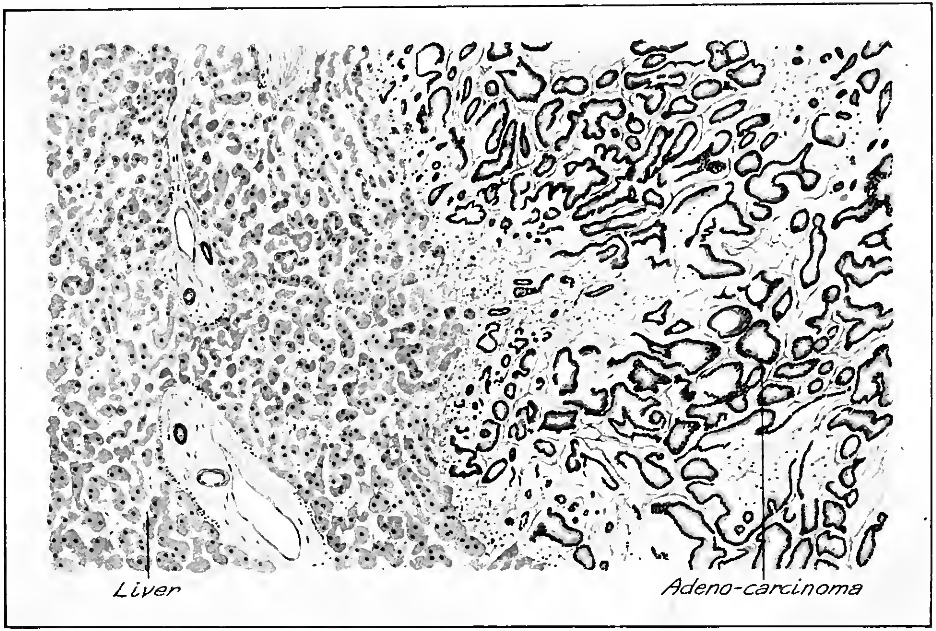

Plate XV.—Secondary deposit of adeno-carcinoma of rectum growing in liver. Note reproduction of structure of rectum and of growth shown in Plate XIV.

cells are closely packed together in solid rods or narrow bands embedded in dense connective tissue, as in the well-known scirrhus of the breast, or they occur in large masses much less closely packed together, with a fine connective tissue, as in the typical soft or medullary cancers. In each there may be very little or absolutely no indication of the normal mammary structure. The connective tissue varies in amount, being much more or much less than normal. It carries the blood vessels as in the normal gland. The vascularity is also disturbed, a great increase in the number of vessels being not uncommon.

The general arrangement of the connective tissue and of the cancer cells gives the appearance of the cells being contained in spaces in the connective tissue. These spaces, which have been termed alveoli—corresponding with the branchings of the masses of cancer cells—naturally communicate one with another, so that the whole structure resembles that of a sponge of which the branching tubules would represent the spaces filled with cancer cells in the case of a malignant tumor. The relative amount of connective tissue or stroma and of cancerous epithelium has led, to a great extent, to the classification of tumors into hard and soft, or scirrhous and medullary. In scirrhous cancer of the breast the connective tissue dominates the picture; in medullary cancer the epithelial cells are much the more abundant element.

All sorts of intermediate stages may be noted with regard to the arrangement of the epithelium, its approach to or departure from that of the normal gland, and the amount of connective tissue. An abundance of solid rods of cancer cells sparsely embedded in an abundant connective tissue gives the "typical" picture of scirrhus of the breast—the commonest and one of the most dangerous of malignant new growths (Plate V). With the tendency to retention of structure, there may be a diminution in the amount of the connective-tissue element (Plate VI), but, as the accompanying figures show, even where the predominating histological picture tends to reproduce the structure of the normal mammary gland, the growth is still malignant, invading and destroying adjacent tissues, and disseminating to distant parts (Plates VII, VIII, IX). A pure adenoma would be regarded as benign, but the term adeno-carcinoma conveys the difficulty of being sure, notwithstanding the microscopical structure, that the growth is really one endowed with malignant properties, as the figures of dissemination by way of the muscle fibers and lymph glands clearly show (Plates X, XI, XII, XIII).

The only other glandular epithelia for which illustrations of the cancerous transformation have been chosen are those of the liver and rectum (Plates XIV, XV, XVI, XVII). The accompanying figures illustrate for them also the essential features described for malignant new growths of the breast. There are, however, growths of which the structure is indistinguishable from the normal, and which nevertheless are highly malignant. The most noteworthy is one occurring in the thyroid gland (Plate XVIII). Notwithstanding its complete resemblance to the normal histology, it is highly malignant, disseminating widely, especially in the bones. (Plate XVIII.)

When a tumor or malignant new growth occurs on a surface, as, for example, of the skin or intestine, the continuous proliferation of cells leads to an increase in surface area, which may have one of two consequences. This increase in surface area may cause a bulging outward, with foldings of the growing area, or the growing portion may extend below the surface. In the first case there is formed a wart-like growth or papilloma (Plate XIX). Such growths are often benign, but are by no means necessarily so, since the warty outgrowth may be combined with a malignant down-growth, for example, in paraffin or arsenic cancer of the skin, in cancer of the lip, in papilloma of the bladder, or in the polypoid growths of the intestines, rectum, and uterus.

When growth proceeds downward at an early stage, the continuity with the normal covering epithelium becomes lost and the growth is sharply defined. The definition becomes more clearly marked by the undermining of the adjacent healthy covering, leading to its exfoliation and the formation of an ulcer over the tumor cells. The simplest case is that of the squamous epithelium covering the tongue where the hairs and glands are absent, their presence complicating the picture for the skin itself (Plates XX, XXI, XXII). The squamous epithelium growing downward produces large masses of an irregular branching nature, sometimes like enlarged and abnormal papilla of the skin, but often rounded or so divided up as to have no connective tissue. In the center of these masses the differentiation to a resemblance to horny material, or keratinization, gives a characteristic picture. This condition is due to the cells not being now on a free surface, owing to the atypical growth. The cells become arranged concentrically, the keratin being in the middle. The appearance is characteristic, and is known as pearl formation.

An exceptional position is occupied by one of the most frequent forms of cancer of the skin, especially of the face, namely, rodent ulcer (Plate XXIII). For a long time it was considered

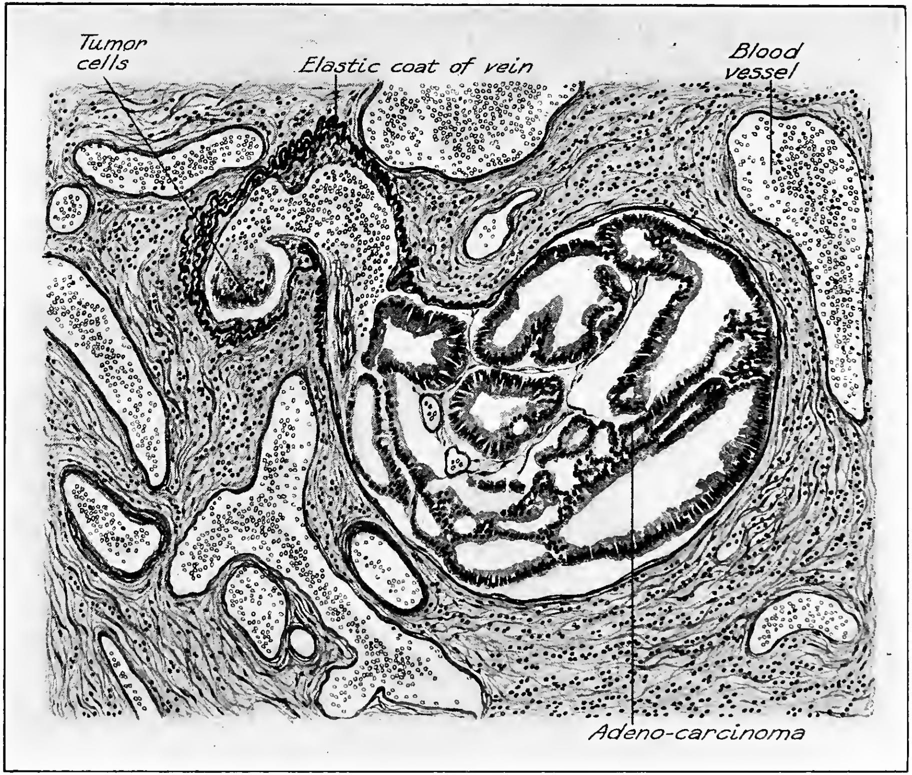

PLATE XVI.—Adeno-carcinoma of rectum spreading by the blood-stream. Blood-vessels in submucous tissue of rectum. One large vein filled with tumor which has partly destroyed the elastic coating.

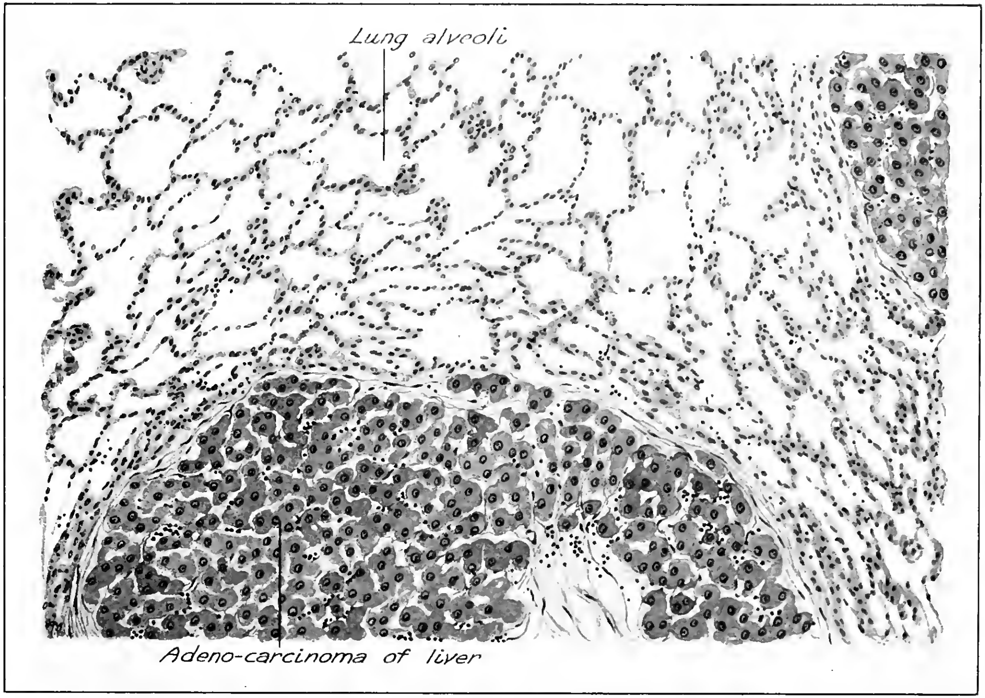

PLATE XVII.—Secondary deposit of adeno-carcinoma of liver growing in the lung. Note reproduction of structure of liver.

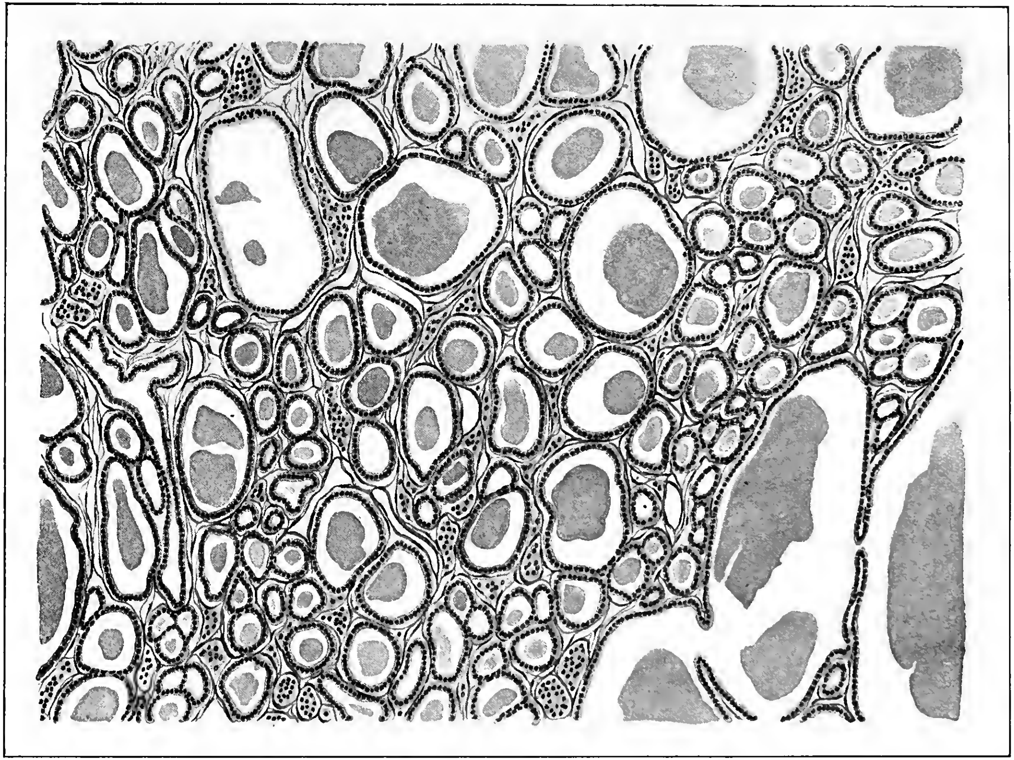

Plate XVIII.—Malignant tumor of the thyroid gland, which, notwithstanding very close resemblance to the normal gland, and production of the typical secretion seen in the spaces, produces secondary growths especially in the bones. Such growths illustrate that what is known as "benign" structure may be compatible with "malignant" behavior.

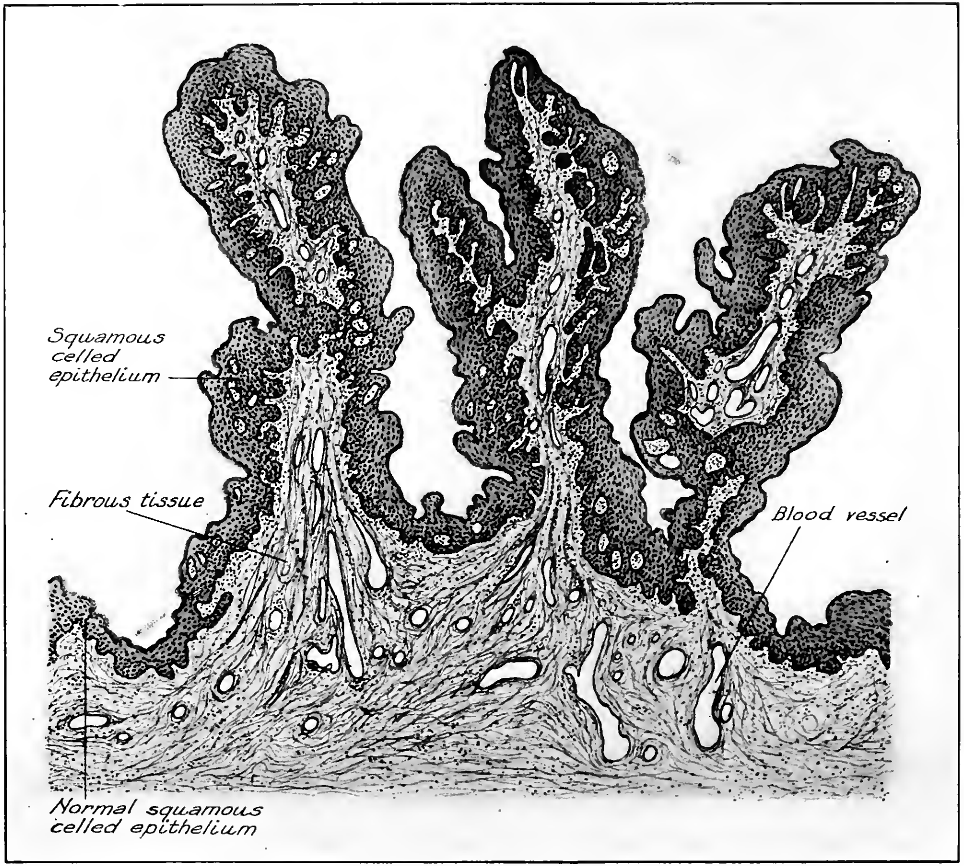

PLATE XIX.—Papilloma of skin. Note in the finger-like processes the retention of the normal relation between surface epithelium and the underlying connective tissue which is not being invaded as is the case in Plate XX.

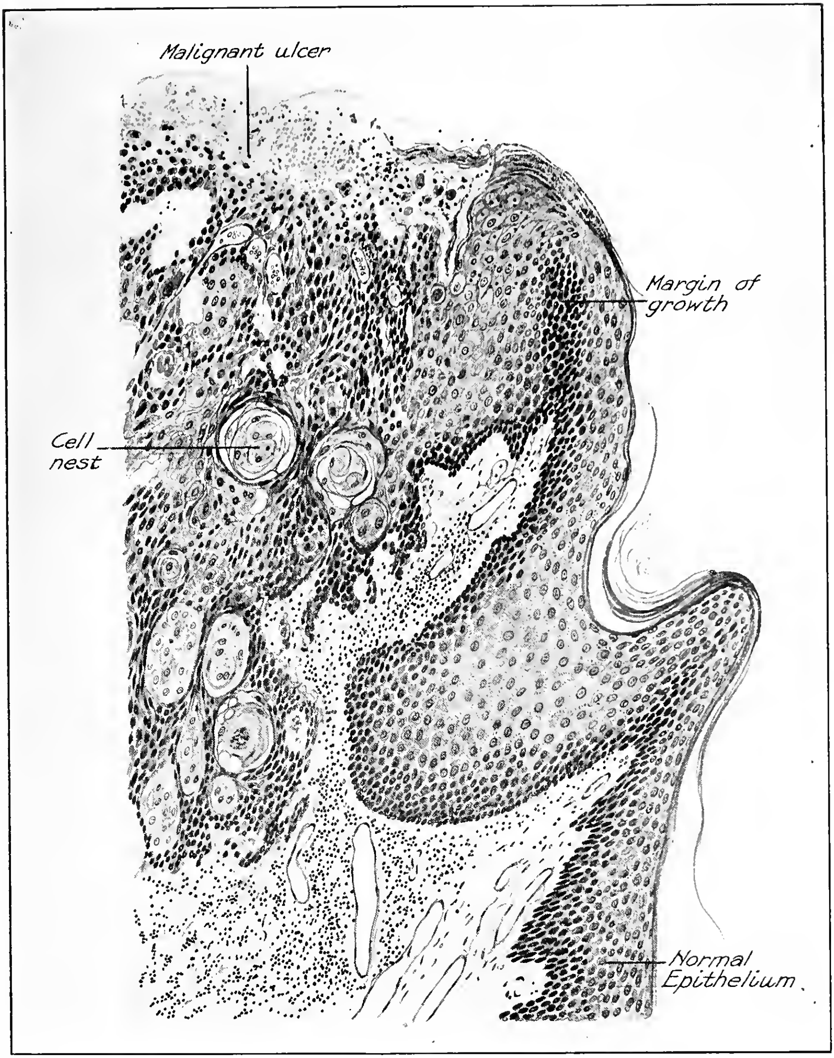

PLATE XX.—Margin of squamous-celled carcinoma (epithelioma) of tongue. Note the down growth of the malignant epithelium, its continuity with healthy epithelium, its liability to ulceration.

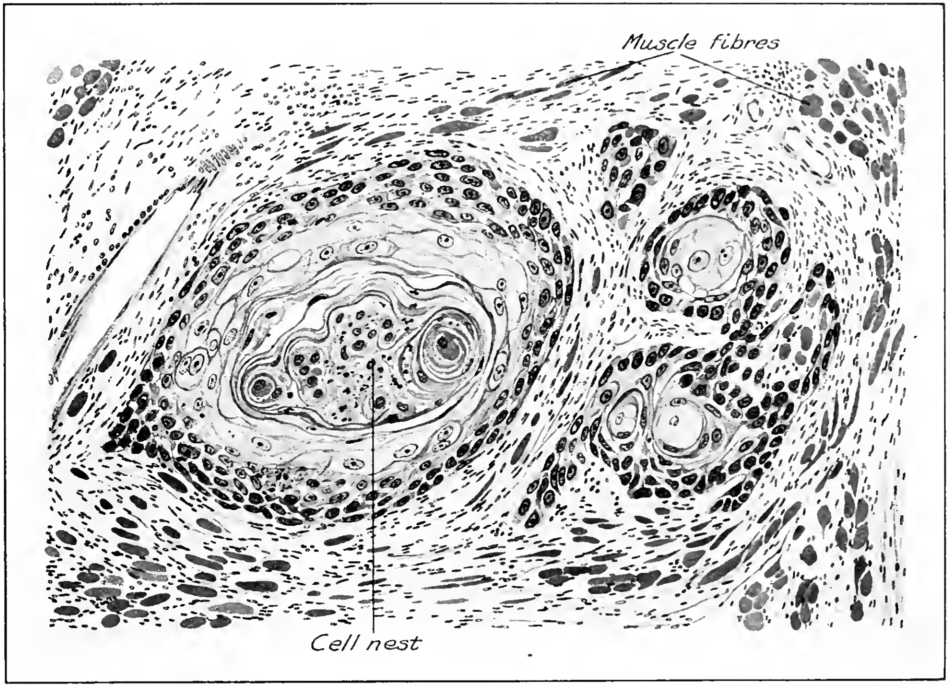

PLATE XXI.—Squamous-celled carcinoma (epithelioma) of tongue spreading between and destroying muscle fibres. Pearl formation well shown.

Plate XXII.—Deep aspect of a small malignant ulcer of the tongue. The cancerous epithelial cells are seen spreading deeply downwards along the muscle fibres, and there is an extensive cell infiltration secondary to the ulceration. This infiltration was the cause of pain and swelling.

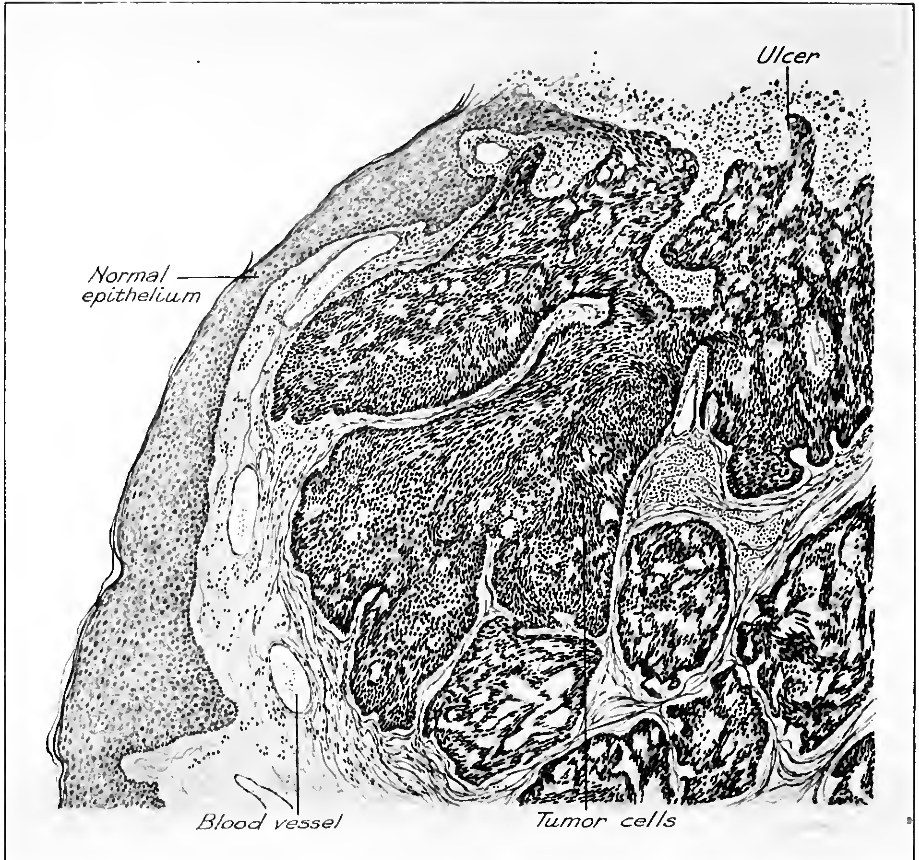

Plate XXIII.—Margin of rodent ulcer. Note the undermining of the skin, which will gradually be pushed off with increase of the size of the ulcer. Note the spindle shape of the tumor cells and their curious arrangement.

doubtful whether or not rodent ulcer really was a malignant new growth. It usually starts in a small, wart-like, red pimple. This speedily breaks down, forming an ulcer, which gradually spreads and which may attain huge dimensions. The cells are devoid of all differentiation and present a peculiar "thatched" arrangement. The tissue of origin is still the subject of debate, the skin itself, the hair follicles, the sebaceous and the sweat glands all being suggested as the mother tissue (Plate XXIII).

CLASSIFICATION

As stated above, practically every tissue of the body is liable to tumors and to cancer. This liability forms to-day the basis for the best working classification; but to understand how it has come to serve this end it is necessary to review briefly how knowledge of normal and pathological histology gradually developed.

The original application of the term "cancer" (Greek *karkinos;* Lat. *cancer*) is shrouded in mystery. It would appear that as certain plants had terms applied to them, like *lungwort* and *liverwort,* because of some fancied resemblance to the lung or liver, so, also, some resemblance to a crab was imagined for certain tumors. The term "cancer," as we have already noted, appears to have been applied originally to cancer of the breast, in which case the enlarged blood vessels, sometimes evident as radiating in the skin from the tumor, may be said to resemble the limbs extending from each side of a marine crab. The origin of the term is of little moment, but it is important to note that at first it had no reference to anatomical or microscopical structure, being applied clinically, and that it continued to be solely so applied until the middle of the last century, or up to the time of Virchow, when the development of morbid anatomy and of the microscopical study of the tissues—histology—opened the discussion as to what was actually meant by "cancer."

In ancient literature there are such excellent descriptions of clinical appearances, notably for the uterus and the breast, that it can scarcely be doubted that they refer to conditions similar to those to which the term "cancer" is applied to-day. But there does not occur, so far as I have been able to ascertain, a single description of the naked-eye appearances to be seen on cutting across a malignant new growth, say a scirrhus of the breast. The old separation into scirrhus, fungus hematodes, etc., was based upon superficial or other clinical features, and rodent ulcer, for example, was so named because it was not recognized as a form of cancer.

Accurate descriptions of the morbid anatomical and of the microscopical or histological appearances are of quite modern date, and are contemporary with the development of microscopical technic, section cutting, and section staining. Prior to 1875, sections were usually obtained without previous hardening (except freezing), and without impregnation in an imbedding material, and were examined, as a rule, unstained, in water or glycerin, or after the application of acetic acid, caustic soda, or teasing or shaking. Many of the terms still in use owe their origin to these primitive methods, notably the use of the term "alveolus" to describe the space in which the cancer cells are held by a surrounding connective tissue. But the relation of the fibrous tissue to the cancer cells was difficult to settle by these crude methods, and led to the view, held by Johannes Müller and Virchow among others, that the connective tissue was the all-pervading matrix out of which both the normal and cancer cells developed, as it were, by crystallization. Many years of discussion, and, notably, the development of embryology, were necessary before the true relation between connective tissue and epithelial tissue was made clear, especially by His. Working with this new knowledge, Thiersch and Waldeyer were able to establish definitely that Virchow and his predecessors were wrong in the opinion which they held as to the development of normal and cancer cells out of a connective-tissue matrix. As is now well known, the epithelial and the connective tissues arise side by side in the embryo at a very early stage. Moreover, the view upheld by His, that the several tissues are specific and do not pass over into one another, except in a few rare instances, and within narrow limits (metaplasia), has been firmly established.

These facts will make it evident why we have to study cancer in connection with the site and tissue in which it takes its origin. Since practically every tissue of the body is liable to tumors and to cancer in several forms, the histological study of tumors and cancer is an even more complicated process than the microscopical study of normal tissues. Nevertheless, the only useful classification of tumors and malignant new growths is a histological one. By employing it, questions of etiology are avoided. Ultimately, when causation has been elucidated, it will form the rational basis of classification.

Thus it comes about that simple tumors are named after the tissues of which they are solely or mainly composed. Tumors of more complex structure are named by combinations of the

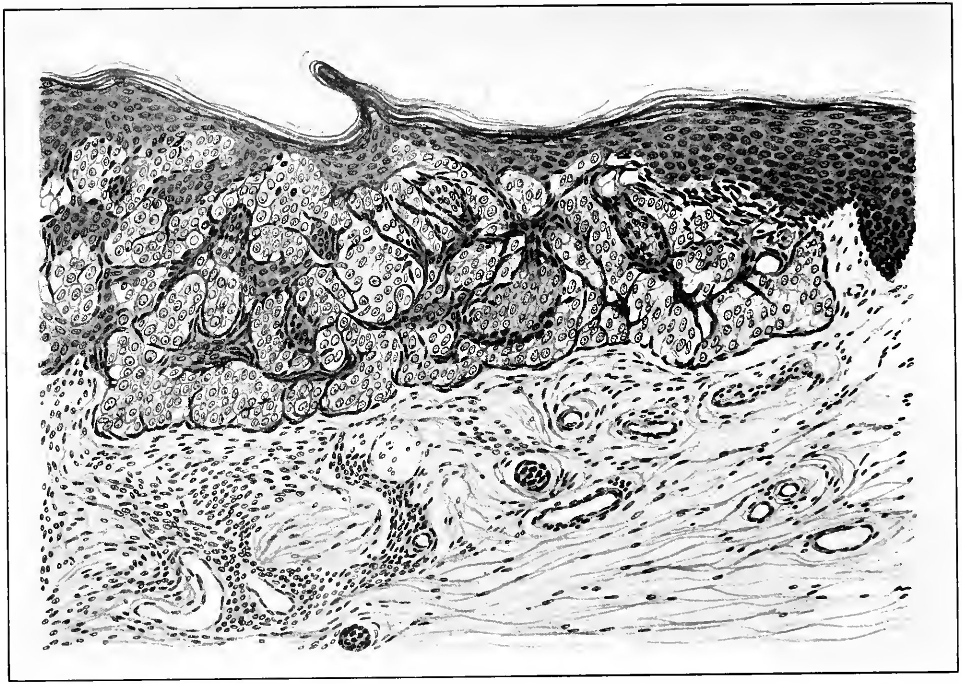

PLATE XXIV.—Paget's Disease (eczema or dermatitis of nipple). The nipple was ulcerated the breast itself extremely affected with solid cancer and the skin covering the breast resembled eczema and had the microscopical appearance shown, viz., clear areas of proliferation of epithelium in the skin itself, and small-cell infiltration under it. There is difference of opinion whether the growth starts in the skin and extends to the gland, or *vice versa*.

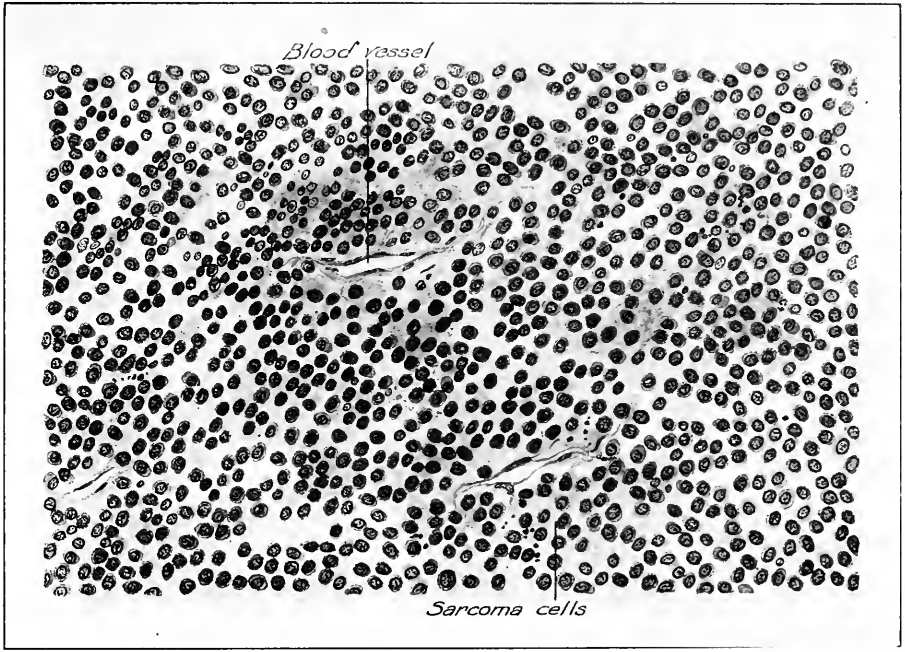

PLATE XXV.—Small round-celled sarcoma.

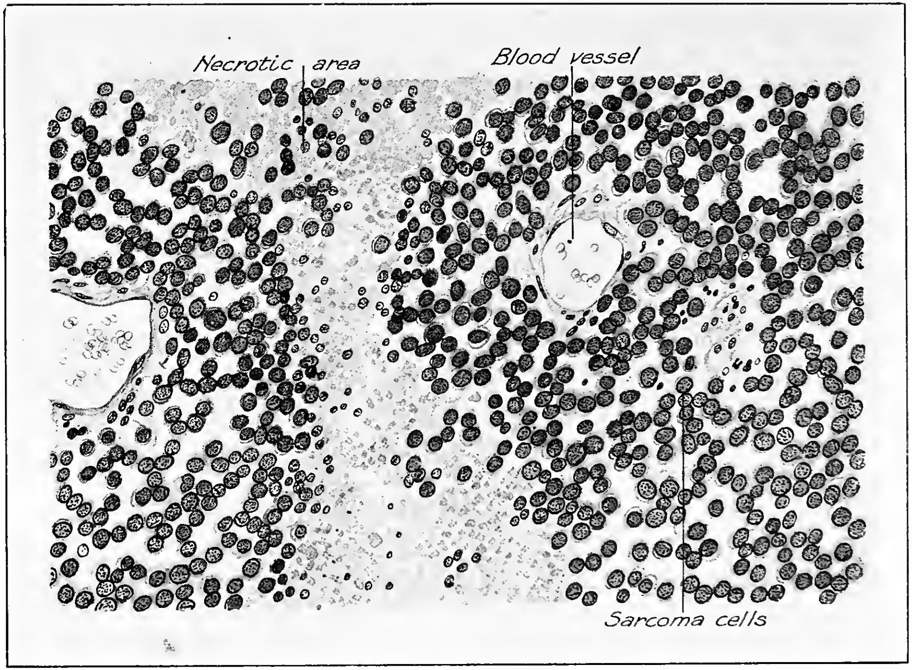

PLATE XXVI.—Large round-celled sarcon a showing marked tendency to necrotic degeneration.

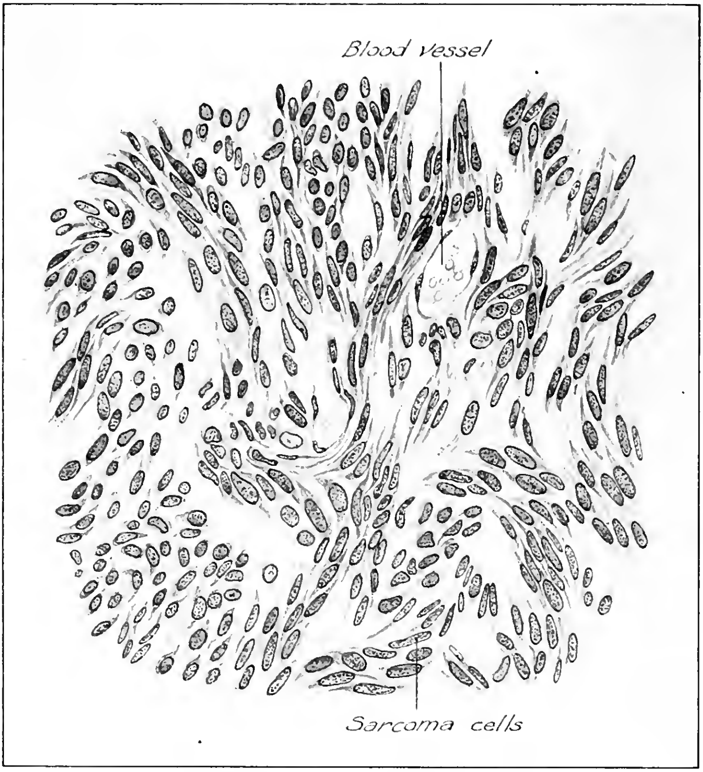

PLATE XXVII.—Spindle-celled sarcoma.

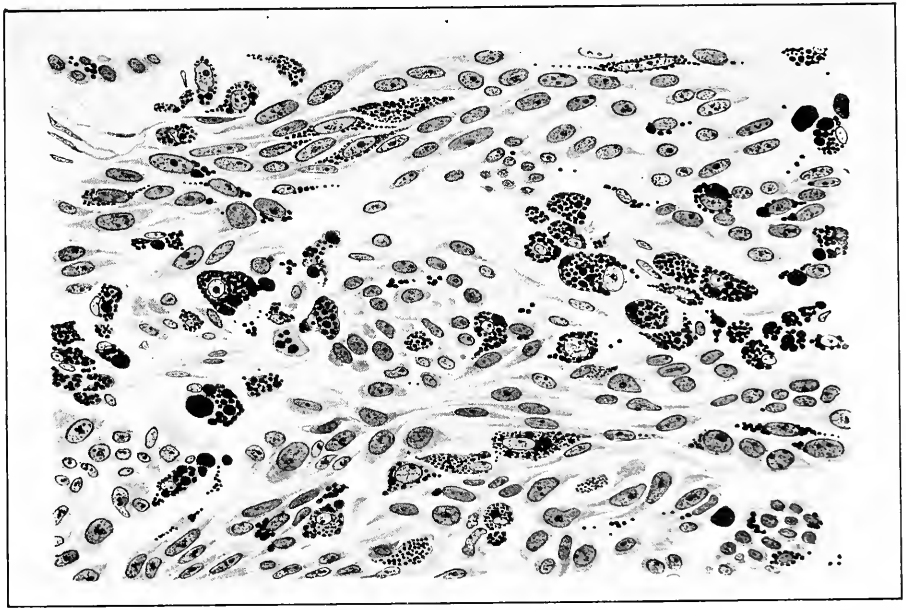

PLATE XXVIII.—Melanotic sarcoma of sole of foot following a puncture. The younger cells are free from pigment, the older cells full of it and other parts of tumor quite black. This small growth had given rise to extensive secondary growths in the lymphatic glands and liver, as shown in Plates XXIX and XXX.

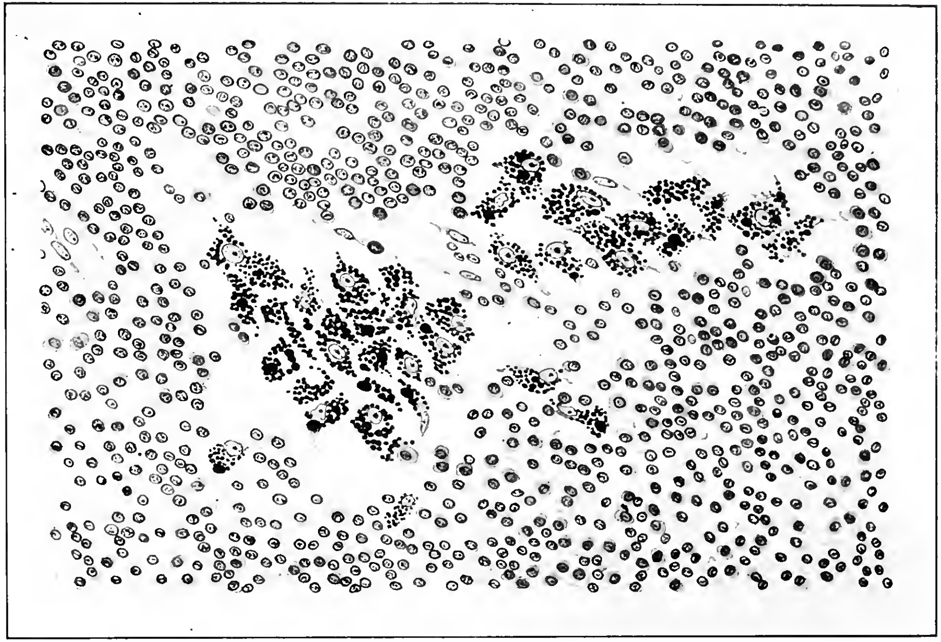

Plate XXIX.—Melanotic sarcoma. Lymphatic gland showing commencement of invasion. Other glands quite black.

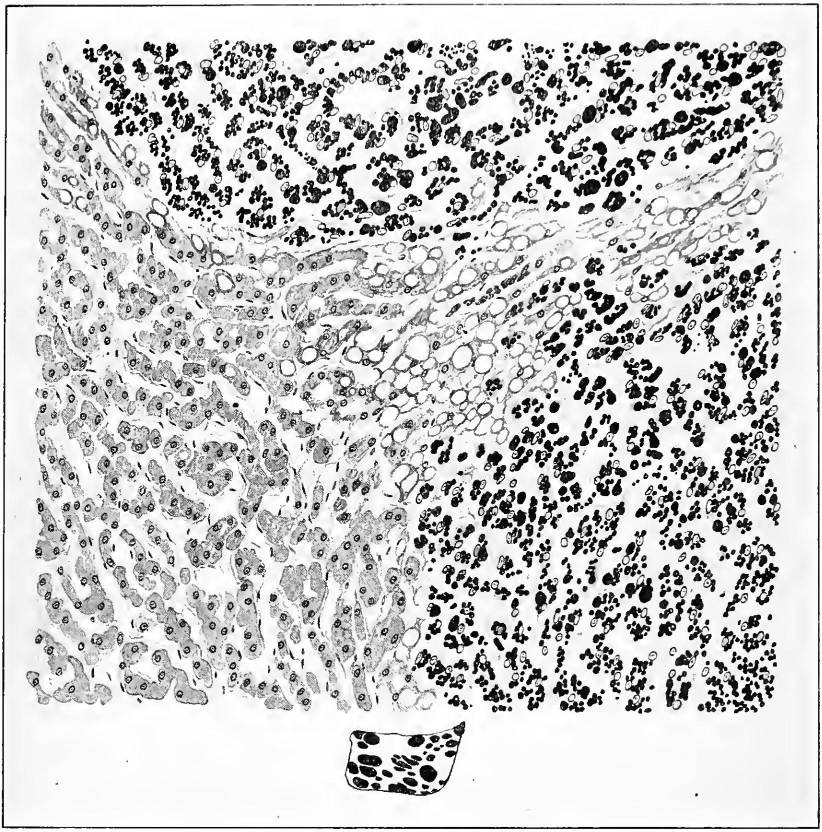

PLATE XXX.—Melanotic sarcoma. Secondary in liver, showing fatty degeneration of liver cells and pressure effects on the liver. Also natural size showing number of secondary nodules in a small piece of liver.

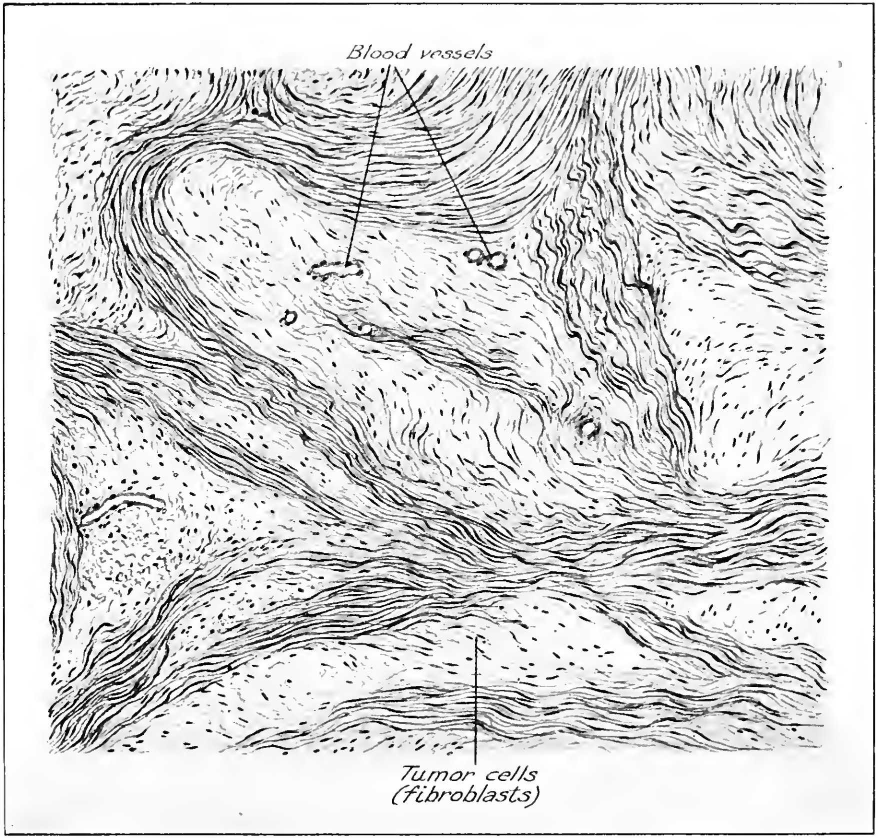

Plate XXXI.—Fibroma. Consists only of dense fibrous tissue with a few vessels.

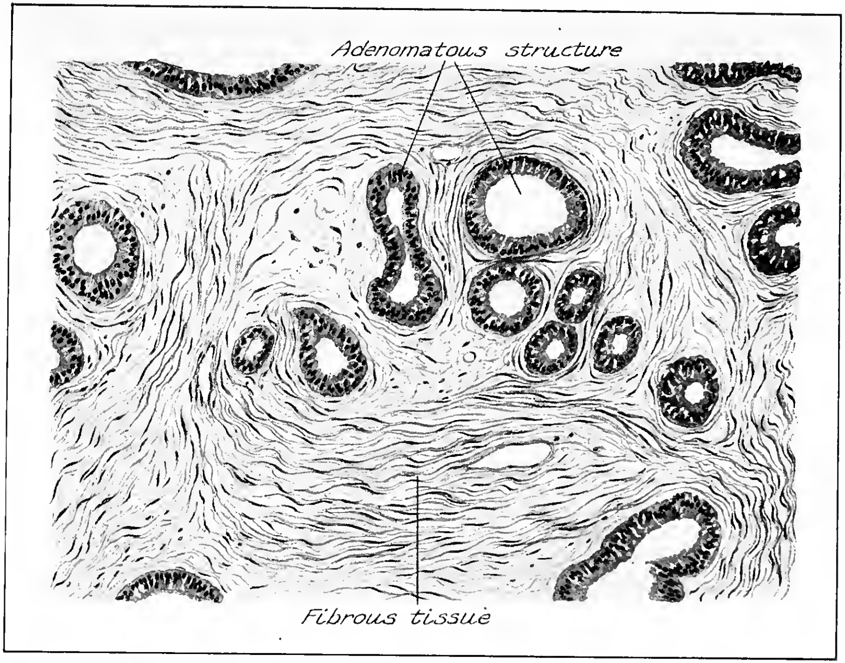

Plate XXXII.—Fibro-adenoma of breast. Note dense fibrous tissue in which gland-like tissue is arranged in tubes or cyst-like spaces of very varying size.

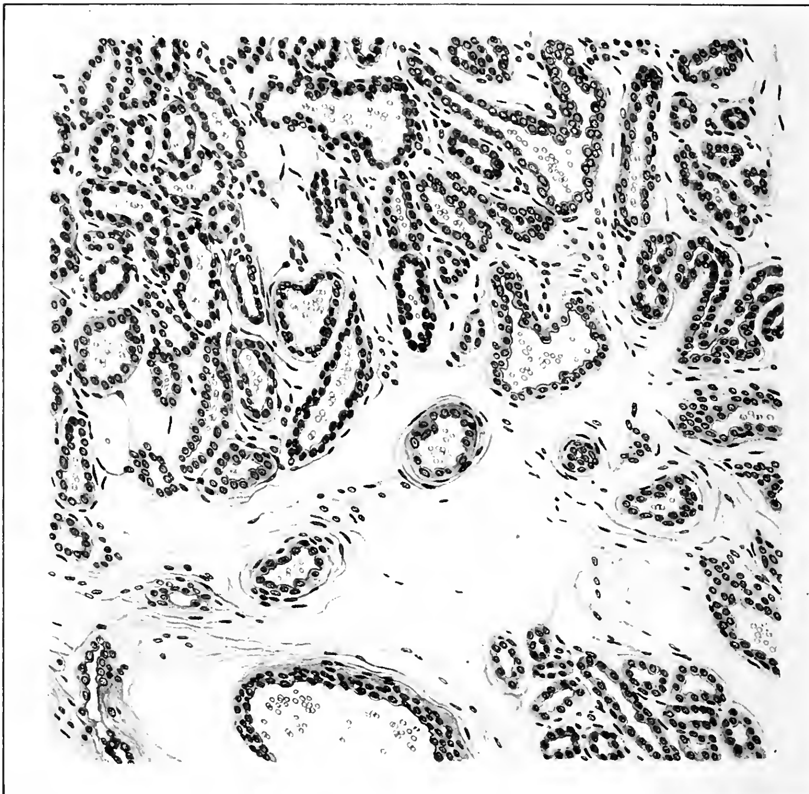

PLATE XXXIII.—Structure of subcutaneous capillary nevus, or birthmark. In the capillary spaces are seen blood corpuscles. Such a nevus may, under chronic irritation or from an unknown cause, become a malignant growth.

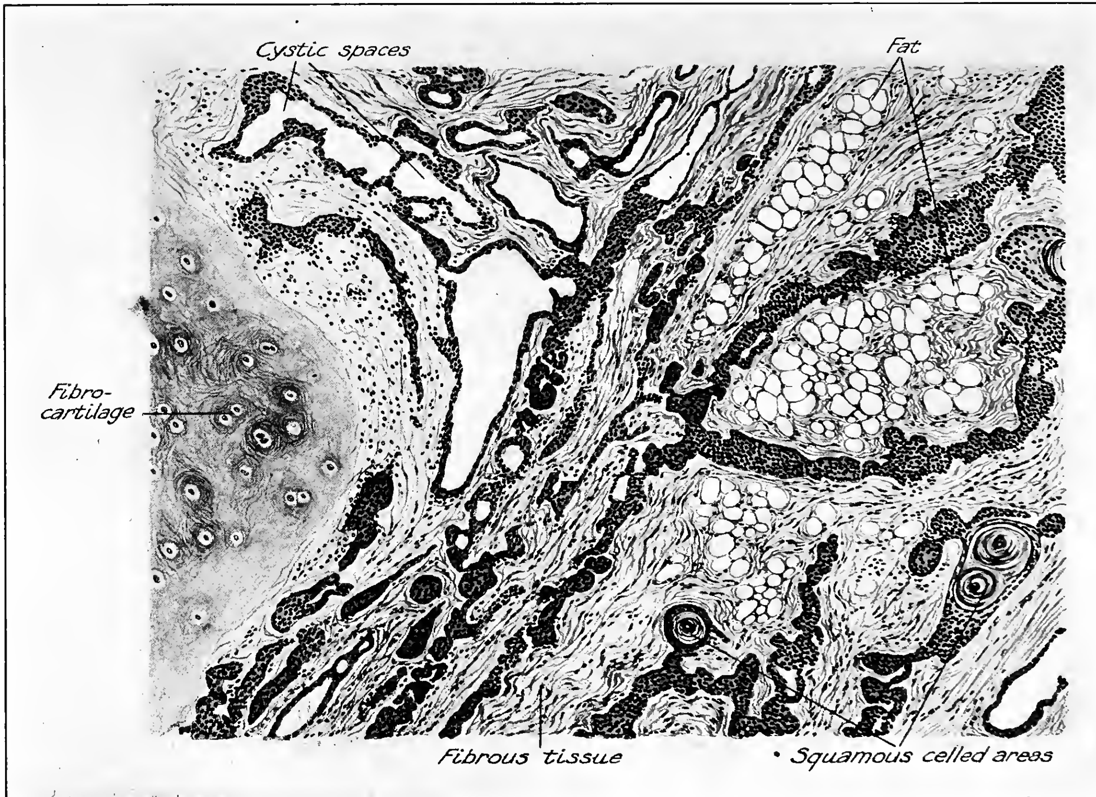

PLATE XXXIV.—Mixed tumor of the parotid region, containing fibro-cartilage and undifferentiated squamous-celled epithelium, cystic spaces lined by epithelium, fat and fibrous tissue.

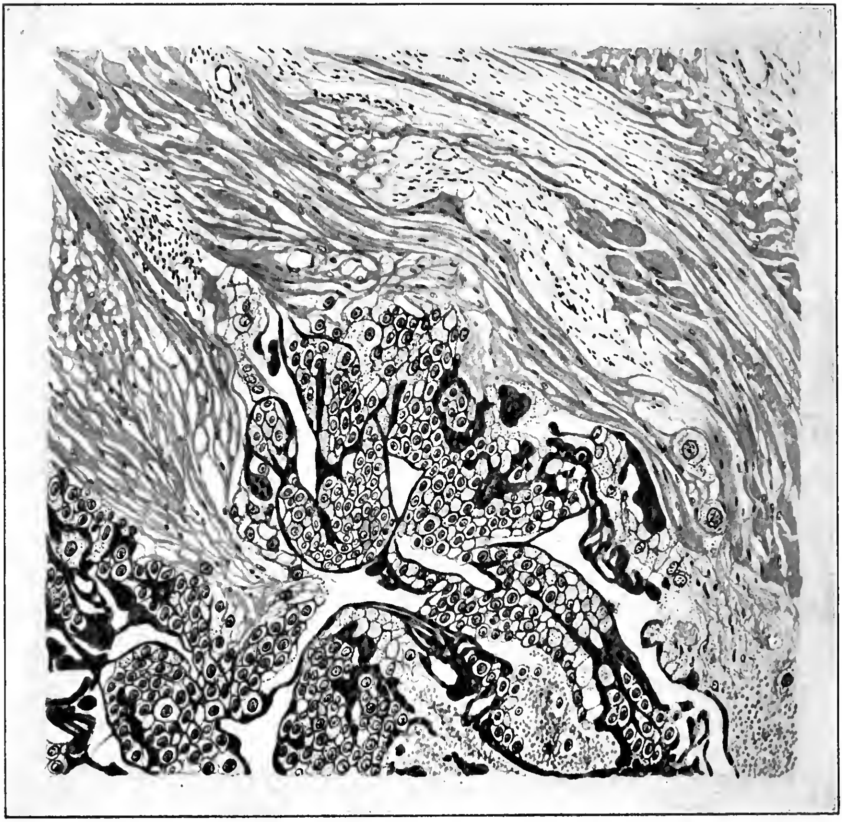

PLATE XXXV.—Chorion epithelioma of uterus. This is a somewhat rare and highly interesting growth arising during pregnancy. It gives rise to numerous secondary growths which often exhibit the remarkable phenomenon of spontaneous healing. The tumor is invading the muscles of the uterus. It shows the characteristic structure of the two epithelial layers of the chorionic villus, viz., the outer darkly staining syncytial layer without definite cell boundaries, giving rise to plasmodial masses, and the deeper layer of Langhans, consisting of large clear cells. The spaces are usually filled with blood.

terms applied to the tissues comprising them. The most complex tumor, in all probability, is the teratoma, which is the result of the inclusion of portions of an imperfectly developed twin in the fully developed organism. When the tumor of any tissue departs largely from the normal structure, it is known as a carcinoma of the epithelial tissue or organ of origin, and as a sarcoma, if it arise in connective tissue. Tumors which apparently arise from the endothelium covering serous surfaces, or lining lymph, and blood vessels, are known as endothelioma.

The following tumors are named in accordance with their tissue of origin:[1]

Fibrous tissue	Fibroma
Cartilage	Chondroma
Bone	Osteoma
Red marrow	Myeloma
Muscle	Myoma
Fat	Lipoma
Mucous tissue	Myxoma
Dental tissue	Odontoma
Nerve	Neuroma
Glia of nervous system	Glioma
Lymphatic gland or tissue	Lymphoma
Blood vessel	Angioma
Lymph vessel	Lymphangioma
Resembling any gland	Adenoma of the particular gland
Resembling wart or outgrowth.	Papilloma or polypus of the particular site.

In the case of the connective-tissue tumors which are malignant, i. e., sarcomata, the adjective malignant may be prefixed. Usually, however, the idea of malignancy is conveyed by combining the terms given above with sarcoma, thus, osteosarcoma, fibrosarcoma. Similarly, when it is intended to convey the idea of malignancy of a tumor of a gland, carcinoma is combined; thus, adenocarcinoma of the breast, stomach, rectum, or other organ of origin.

The connective tissue of a tumor, as explained below, is partly inherent in the tumor itself, it is partly derived from the preëxistent connective tissue of the surroundings, and it is partly a new formation. All connective tissues, with the excep-

[1] Illustrations of many of these appear in the foregoing Plates, as well as in Plates XXIV to XXXV.

tion of bone and cartilage, may serve as a scaffolding, and their nature and amount may lead to tumors being classified, for example when fibrous tissue forms an important part of the growth, as fibrosarcoma, fibrolipoma, or fibro-adenoma. When both the epithelial and connective-tissue components of a tumor exhibit malignant properties, it is customary to speak of a mixed tumor or a carcinoma-sarcomatodes.

ORIGIN AND SPREAD

Histological study, confirmed by the experimental inoculation of cancer cells, has now definitely established that cancer arises in a minute circumscribed area where a progressive proliferation of cells takes place. There is usually only one center of growth, but there may be several, which ultimately coalesce within a minute area. It is rare, and indeed it has been denied, that cancerous transformation of an entire organ occurs. It must be remembered that histological study tells us little or nothing as to the biological change which starts the cancerous proliferation.

The consequences of the progressive proliferation are local and remote. A lump may form locally, or an ulcer may develop. The lump is found, on microscopical examination, not to be encapsulated, and the ulcer is not sharply defined at its base and sides; both fade off into the surrounding tissues because they have been infiltrated by the growing cells. Actual destruction of tissue may have occurred, especially of a covering skin or mucous membrane, of a bone or of a cartilage. These, although not affording a scaffolding for cancer cells, as does connective tissue, do not become incorporated in the malignant growth. The cancer cells penetrate between and destroy muscle fibers by pressure, thus causing disorganization of muscles. The columns of cancer cells may actually spread along inside the sheath of the muscle fibers. They get into the blood vessels, especially the veins, the stronger elastic coat of the arteries being more resistant. They spread along the lymphatic channels either with or against the lymph stream. Both in the veins and lymphatics particles may be carried away and lodged in distant parts, or growth may take place by continuity, as described by Handley in his "lymphatic permeation" theory. (See Section XI, Chapter 2.) These growing points, as it were, thus proceed ever farther and farther from the parent tumor.

Remote consequences may occur, therefore, anywhere; but their relative frequency in any particular site is determined by the lymphatic or vascular connections of the site or organ primarily attacked. Thus, owing to the fact that the cancer cells are carried to the liver by the portal system after they have entered the large veins in the submucous tissue of the bowel, the liver is the common site of secondary growths from the rectum or the intestines. The lung is another frequent site for secondary growths, extension in this case taking place through the lymphatics or blood vessels, or through the blood stream by way of the thoracic duct When extension takes place through the lymphatic channels, the lymphatic glands are attacked in consequence.

Some growths manifest a tendency to the formation of secondary deposits in the bones. Thus colonies arise from transplanted cells and then reproduce in their new surroundings all the features of the primary growth, so that, as it has been briefly expressed, a piece of rectum is found growing in the liver, liver in the lungs, mamma in lymph glands or bones, and skin in lymph glands or lungs. These exhibit also all the destructive and infiltrative properties of the primary growth, invading in their turn and destroying the tissues of the important organs in which they have established themselves, causing the destruction of blood vessels and giving rise to hemorrhages, leading to ulcerated surfaces and to abscesses, destroying bone and leading to spontaneous fractures, settling in the brain and producing unconsciousness and other disturbances.

BASIS OF SURGICAL TREATMENT

Thiersch and Waldeyer demonstrated that carcinomata are derived from preëxisting epithelium, and not, as held by Virchow, from connective tissue. They thus dealt the last and final blow to the old views concerning the constitutional nature of the disease—views which had caused surgeons to despair of successfully treating a "blood disease" by surgery. The first consequence of this change of view was the establishment of the fact that the secondary growths which appear in other parts of the body are the result of the transplantation there of cells from the original focus, thus setting up a fresh colony, and that they are not the result of some influence, proceeding from the primary tumor or pervading the constitution, whereby a transformation is effected in the normal tissues of the parts so attacked.

Thus the surgical treatment of cancer came to have a rational basis, namely, the removal of the primary focus before any spread had taken place, or, at any rate, before it had extended beyond the immediate neighborhood. Waldeyer[1] recommended the removal of the entire mammary gland, because he thought if one part of an organ had shown itself liable to cancerous change, then the rest, if left behind, would likewise ultimately undergo a similar change. Since that time the doctrine of the circumscribed area within which cancer arises has been established as the general rule, and to-day the surgical practice of wide removal is based not so much, and often not at all, upon the fear of the liability of the organ as a whole to the disease, as upon the recognition of the necessity for removing the primary focus, together with all the tissues to which there is any possibility of its having already sent offshoots. As long ago as 1867, Charles Moore[2] was of the opinion that recurrence after an operation was not due to constitutional taint or to cancer being a "blood disease," but to incomplete removal of the primary tumor and its secondary offshoots. It will be remembered that this view was put forward before Lister had triumphed over sepsis. It is therefore not surprising that the view, and the extensive operation which Moore based upon it, met with strong opposition for years. In a great debate in 1874, before the Pathological Society of London, the above innovations were hotly contested.[3] The late Sir James Paget, among others, championed the constitutional or "blood disease" theory as against the circumscribed origin upheld by Moore and de Morgan. Since that time correlated histological study and surgical achievement have established the fact that cancer arises in a minute area which can be excised, and that by thus removing this area the patient may be cured. The experiments of the Imperial Cancer Research Fund have proved that all the features of the disease can be reproduced by implanting the minutest fragment, thus giving additional foundation for modern surgical practice as applied to cancer.

SUMMARY

The development of knowledge concerning the histopathology of cancer, and the experiments which have proved the trans-

[1] Waldeyer, W.—"Ueber den Krebs," Vollkmann's *Sammlung klinischer Vorträge*, No. 33, 1872.

[2] Moore, Charles.—"On the Influence of Inadequate Operations on the Theory of Cancer," Trans. Royal Med. Chir. Soc., London, 1867.

[3] Trans. Path. Soc. of London, Vol. XXV, 1874.

plantability of cancer tissue, have had a most important bearing upon the treatment of the disease, establishing, beyond question, the view that the complete surgical removal of the primary focus results in the eradication of the malignant process and in the cure of the patient. It is therefore greatly to be regretted that the public is encouraged to give ear to old discarded views which to-day are still put forward as if they were new, and which appeal with especial force to the ignorant and to the timid who fear "the knife."

SECTION VI

CANCER RESEARCH—A RÉSUMÉ OF THE WORLD'S WORK

PRACTICAL RESULTS

The Failure of Modern Experimental Study of Cancer to Establish the Etiology of the Disease.—Before considering the net results of the modern experimental investigation of cancer, it is well to recall the fact that in the essential matter of etiology no entirely new or revolutionary conceptions have been evolved. Cancer continues to offer an exception to the general rule of the gradual change in the prevailing views concerning the causation and treatment of diseases. It likewise fails to come within the category of the revolutionary change in the conception of etiology and treatment which has marked the discovery of the infective nature of many diseases.

Dominated for centuries by primitive humoral ideas of disease, it was only in the middle of the nineteenth century, and largely owing to the work of Virchow, that, by observation, facts were established on a basis sufficient to permit students of morbid anatomy, and, later, students of morbid histology, to pursue paths of their own.

Leaving medieval dogma and humoral conceptions of cancer out of all account, and considering only those hypotheses which are of modern importance, there has been, in the whole medical history of cancer, no more dramatic clash of theory with fact than that which caused Virchow [1] to cease the publication of his "Onkologie" (see Section IV, Chapter 1, p. 108), in consequence of the appearance of the papers of Thiersch,[2] whose views were confirmed and extended by those of Waldeyer.[3] That

[1] Virchow, Rudolph.—"Die Krankhaften Geschwülste," Berl., 1863, Vol. II, Onkologie, Part I.

[2] Thiersch, Carl.—"Der Epithelialkrebs, namentlich der Haut. Eine anatomisch klinische Untersuchung. Mit einem Atlas mikroscopischer Abildungen," Leipz., 1865.

[3] Waldeyer, W.—"Die Entwicklung der Carcinome": Virchow's Archiv, XLI, 1867, No. XXIV, p. 470; *ibid.*, LV, 1872, pp. 67-159; "Ueber den Krebs": Sammlung klin. Vorträge, No. 33, 1872, pp. 163-196.

event marked one of the final breaks from the old belief in the humoral nature of cancer. Another event of importance was the gradual emancipation of investigators from the idea that cancer must of necessity be due to an inherited dyscrasia or "condition of the blood." The freedom thus obtained has led to the study of cancer by innumerable workers in the autopsy room and in the histopathological laboratory.

The final result of the clash between dogma and fact may be said to have resolved itself into an agreement that cancer is *local in its beginning.* There remained, however, a difference of opinion as to whether or not the increase in the size of the original small area affected is the consequence of the communication of the disease to adjacent tissues. Thus two sharply opposed schools have arisen, holding, respectively (1) that there is a progressive transformation in the adjacent tissues (appositional transformation), and (2) that the increase in the size of the affected area is due to the progressive growth of the cells primarily attacked and to the displacement by them of adjacent tissues. This discussion was pursued, without final result, up to the time of the establishment of experimental study upon animals.

In the past twelve years conflicting views on the nature of cancer have been subjected to the impersonal arbitrament of experiment. By this means a judgment has been obtained entirely favorable to the endogenous origin of cancer from the tissues with which it grows in continuity, and in which it has its primary site. In this respect experiment may be said to have but confirmed conclusions arrived at in 1867 by Waldeyer, who, while generously acknowledging the work of others along the same lines, concluded that all primary carcinoma arose by growth in continuity from the covering epithelium, and metastases, by the growth of fragments transported by the blood or lymph streams. Waldeyer extended these results to the sarcomata.

The results of experiment go further, however, than merely excluding all conclusions other than that a malignant new growth is part and parcel of the body of its host; they permit a choice to be made among many alternative views concerning the manner in which cancer is derived from normal tissue. These have been considered in the section of Histopathology.

Experiments on mice demonstrated very early that it was necessary to separate the problem of the genesis of malignant new growths from that of the conditions suitable for growth; that is, from the causes which determine mere increase in size and extension in the animal primarily affected.[1] Transplantation was shown to be essentially similar to the process of metastasis as it occurs in the individual providing the spontaneous tumor. The experimental transmission of carcinoma showed that, while conditions leading to the initiation of malignant tumors were relatively infrequent, once begun, this cancerous proliferation, under favorable conditions, could persist for a long time unaltered; and could give rise to masses of tissue of great size in a large proportion of healthy animals, quite unhampered by the restrictions which determine the growth and limit the size attained by adult organisms.[2]

The value of studying, for its own sake, the problem of growth as presented under experimental conditions has been an incentive to much investigation, especially by the workers of the Imperial Cancer Research Fund, London, and of the Royal Prussian Institute of Experimental Therapeutics, Frankfort-on-Main.[3] They have recognized the value of the opportunities afforded by such study for obtaining indirect knowledge of the nature of cancer, and each school has made guarded inferences as to etiology. By a study of *how* cancer grows, each has hoped to obtain knowledge of *why* it grows. According to their conceptions the processes of growth present a rational starting point for the study of some of the problems of cancer, but Ehrlich and his associates on the one hand, and Bashford and his coworkers on the other, have arrived at divergent conclusions.

In the human subject only the stage at which a tumor has arrived can be subjected to clinical and pathological or microscopical examination; the stages through which it has passed and those through which it may pass in future are necessarily left to the imagination. The discussion of any influence which surrounding tissues, or the body and its fluids as a whole, may exert on the process, is equally hypothetical. So far as the fully developed cancer-cell permits, these gaps may be and already have been partially filled by experiment. Only by experiment, supported by knowledge previously acquired through morbid anatomy and histology, has it been possible to come to certain unequivocal conclusions, such as the following:

[1] Bashford and Murray.—"The Significance of the Geographical Distribution of Cancer," First Annual Report, Imperial Cancer Research Fund, London, July, 1903.

[2] Bashford and Murray.—"The Significance of the Zoölogical Distribution, the Nature of the Mitoses, and the Transmissibilty of Cancer." Proc. Roy. Soc., Vol. 73, Jan. 12, 1904.

[3] Ehrlich, P.—"Experimentelle Karzinomstudien an Mäusen," *Zeit. f. Aertzl. Fortbildung*, 1906, III, 205; *ibid.*, Arbeit. aus dem Kgl. Inst. für experimentelle Therap., Hft. 1, 1906, p. 75.

The "Individuality" of Cancer Established by Experiment.—From the study of tumors in animals spontaneously affected, as compared with those in normal animals which are the hosts of transplanted tumors, it has been considered proved that the tumor is peculiar to the individual in which it arises, containing nothing demonstrably extraneous. From the study of the life-history of tumors, as made possible by prolonged propagation, the morphological and biological metamorphoses of which tumor-cells are capable have been clearly demonstrated. For all that was known to the contrary, the undifferentiated, "embryonic" tissue of a cancer might have exhibited typical differentiation promptly after transplantation in the way that transplanted embryonic tissues do; that this did not occur in the case of cancer shows that mere arrested growth of embryonic tissue is not a sufficient explanation of the origin and nature of cancer.

The individuality of cancer has long been maintained, under various guises, on the basis of deductions drawn from the histological examination of the tissues at the site of the primary lesion and on those of the nature of the secondary or metastatic formations. It has also been as vehemently denied. When every consideration is paid to the evidence and arguments which have been adduced for or against the idea of the individuality of cancer, it must be admitted that the purely microscopical findings in themselves were insufficient for decision in all the points in question. Although the advocates of an extrinsic (parasitic) genesis were never able to convince their opponents, the pathological anatomists, the latter were also obliged, on their part, to confess that they did not absolutely refuse to admit the possibility of an extrinsic parasitic etiology.

By the simple process of inoculating a bit of cancer tissue, and by observing the local growth and dissemination of the same, long and patient experiment has ultimately supported the view that all the characteristics of cancer may be explained by consequences emanating from a small circumscribed area. For reasons quite different from, and independent of, those advanced by pathological anatomists, investigation of propagated cancer has advanced to two conclusions exceeding all others in theoretical and practical importance: A malignant new growth arises (1) in a circumscribed area, and (2) for reasons particular to the host as an individual.

A portion of malignant tumor, transferred to another part of the body, is usually extremely dangerous to the individual. Transferred to the body of another subject, it is very rarely dangerous to the new host, and then only under conditions which obtain in experiments upon lower animals.

Experiment appears to have limited the genesis of cancer, more strictly than before, to a combination of causes peculiar to each individual and perhaps to the reaction of his tissues to extraneous irritative agencies, a susceptibility to which may be inherited, as shown in the section on Statistical Considerations. Experiment likewise indicates, with equal emphasis, that no one case of cancer has any direct relation to another, as is also pointed out in the section on Statistical Considerations.

If this be true, then the question may be asked—Why propagate cancer? To grow cancer indefinitely is simply to retire farther and farther from the genesis of the disease. For many experimenters, propagation is sufficiently justified as being an indirect way of attacking a problem which hitherto has defied all frontal attacks, while at the same time, it is an objective method of studying the biology of tumor cells.

Leaving out of consideration those experimental exigencies which may be met only by having constant sources of tumor material, and leaving for reference later the indirect bearing of the study of propagation, some of its other advantages may be noted.

The Possibility of Transference no Proof of Infectivity of Cancer.—The circumstances under which cancer may be transferred artificially from one animal to another are now accurately known. The strict limitations under which this is possible, even when the experimental conditions are most favorable, are such that, for practical purposes, the danger of natural transference does not require consideration, and is not even of sufficient importance to merit debate as an academic question. It is worth while, however, to endeavor to dispel a certain amount of confusion which prevails among many who, having no practical experience with reference to the experimental transmission of cancer, are unable to interpret its significance.

As a rule the transference of a primary cancer is very difficult, and must not be confounded with the transference of a propagated cancer. In the former case a growth is removed from its natural environment and placed in strange surroundings. The cancer-cell rarely survives this procedure. In the latter case the difficulties of the first procedure have been artificially surmounted, the cancer-cell is no longer a natural one, but one adapted to transference, which, in some cases, but even then by no means always, may be easily performed.

There are two important points to be borne in mind with reference to the inoculation of cancer. First, should transference be held to indicate a cause of the great frequency of cancer, the reasoning must start from the difficulty of transferring primary tumors, and not from the ease with which some artificially propagated tumors may be transferred. Second, transference is effected by the implantation and continued growth of living cancer-cells only. To assume that such an engrafting of cells peculiar to each species, yet parasitic for each, occurs in nature, not only from one individual to another, but from one generation to another throughout the vertebrates, postulates that it has occurred throughout unknown geological ages, and presupposes also the existence of an animate world of which biology knows nothing. A little reflection at once shows the absurdity of such an assumption. Nevertheless, it is entertained by some who do not sharply differentiate between *infection* and the *implantation or grafting of living cells.*[1] According to their view the implantation of cancer from one generation of mice to another is an experimental reproduction of relations existing in nature. This involves a grave fallacy. It is now universally agreed that experimental cancer is neither more nor less than the grafting of the tumor of an animal (part and parcel of whose body it was) into the same animal or into others to which it is alien.

Apolant[2] writes that the cultivation of a true tumor of the dog has been performed successfully by Bashford; that this observation has importance because it proves that the transplantation through series of animals is not peculiar to the growths of the rat and mouse, but is shared by the higher animals. Therefore the objections raised that the tumors of the mouse and rat are fundamentally different from those of other animals, for example, the dog and man, have no basis in fact.

The "Limitless" Growth of Cancer.—Before the experimental era the growth of cancer was loosely spoken of as "limitless," although it terminated with the death of the individual organism attacked. No single fact of itself reveals the fundamental problem so clearly as does the continuous growth of tumors when transferred from one animal to another over a period of time exceeding the duration of the lives of many successive generations of animals. It has been pointed out that the enormous amount of growth obtained by artificial propagation is a problem new to the biology of vertebrates, and that the successive cell generations are comparable to growth as seen in

[1] *Infection* signifies the transformation of normal into diseased tissues through the intervention of micro-organisms. The *implantation of cancer cells* does not effect any such transformation.

[2] Apolant, Hugo.—"Die experimentelle Erforschung der Geschwülste," Handbuch der pathogenen Micro-organismen. Herausgeben von Kolle und Wassermann. Bd. III, 1913, p. 176.

the continuity of species, rather than to that of individual animals; as, for example, a mouse, a rat, a guinea-pig, a rabbit or a dog; these being the animals in which unquestionable tumors have been or are at present being propagated in different parts of the world. Bashford and Murray likened the bulk of mouse tumor which they had produced by 1905 to a mass greater than that of an elephant, and in 1906 Ehrlich calculated that his experience signified the speedy production of a mass exceeding that of the sun.

The study of propagation, however, is also of interest in itself. Are any limits of time or amount set to it, such as are set to the other activities of vertebrate organisms—for example to the length of life itself, or to the length of the gestation period? Does it give indications of how it originated or how it is maintained? Do tumor-strains of different origin, and otherwise distinguishable at the outset of propagation, advance during their continuation to a common type, either in morphological characters or in biological behavior, under the influence of a constant environment? Is growth purely vegetative, or is it renewed from time to time? Some of these questions were raised many years ago as the result of the microscopical study of cancer in man. Experiment has only recently replied to some of them; others have been answered only in ambiguous terms.

The Bearing of the Study of Propagation upon Other Phases of the Cancer Problem.—The propagation of cancer has thrown light upon the spontaneous healing of natural cancer in human beings. The study of this important phenomenon, either as it occurs during propagation or in primary tumors in animals, points to the primordial moment of phases in the life of the tumor-cells. Propagation has revealed phases in the susceptibility of the tumor-cells to the extracellular factors accompanying spontaneous healing.

The Microscopical Demonstration of the Facts of Transferring Cancer.—The successful inoculation of cancer—carcinoma and sarcoma—had already been made in rats and mice; but was neglected and misconstrued. It was therefore reserved for Jensen, in 1902, in the case of carcinoma of the mamma of the mouse, to obtain full recognition for work which clearly demonstrated true transplantation or grafting. In the case of carcinoma previous work by Hanau [1] and Morau [2] had not been

[1] Hanau, A.—"Erfolgreiche experimentelle Uebertragung von Carcinom," *Fortschr. d. Med.*, Berl., 1889, VII, 321-329.

[2] Morau, H.—"Recherches expérimentales sur la transmissibilité de certaines neoplasmes (epitheliomas cylindriques)," *Arch. de Méd. exper.*, 1894, 677.

carried out with such great attention to detail; and in the case of sarcoma the results had been imperfectly or ambiguously described, largely owing to the difficulty of dealing with sarcomata as material for experimental observation. The experimental reproduction of all the features of natural cancer was completed by the observations of Borrel and Haaland, but mainly it was the result of some years of study on the part of the workers of the Imperial Cancer Research Fund. These investigators demonstrated in 1905 that out of the minute particle of tissue inoculated there were developed, with one and the same tumor strain, not only a local tumor, but also expansive or benign and infiltrative or malignant growths, as well as secondary growths in internal organs and the lymphatic glands, terminal cachexia and death. In succeeding years the workers in this laboratory, notably Haaland and Murray, have added all the details necessary to complete the analogy with the malignant new growths in man.

Propagation Experiments Justify the Surgical Treatment of Cancer.—This experimental reproduction of all the features of the natural disease has proved conclusively that growth takes place, not by converting healthy cells into cancer cells, but in consequence of the proliferation of the cancer cells introduced. Furthermore, it has established the fact that if the cancer cells are surgically removed early enough after inoculation, all evil effects are obviated. Thus experiment has absolved the surgical treatment of cancer from the last vestiges of the charge that it is unjustifiable, and that, at best, it is a mere empirical proceeding. This is perhaps the most valuable practical result yielded by modern cancer research. Surgical removal is as yet the only sure way in which an animal can be protected against the ultimate consequences of inoculation with cancer-cells.

The Infectivity of Cancer in the Light of Propagation Experiments.—Modern cancer research has yielded no evidence of the communicability of the disease by infection, and much fresh evidence that this is improbable; while there is quite definite proof that the cause of the great frequency of cancer is not the transplantation of cancer-cells from one person to another.

Bearing upon the last point, among many others, three very important facts may be mentioned: (1) The housing of cancer animals in large numbers with others has not led to any epidemic. (2) It has been found possible to protect all animals against the inoculation of a tumor from other animals of their own species, but it is quite impossible to protect the animal in which the tumor developed naturally against reinoculation with its own tumor. (3) While it is possible completely to protect animals against an inoculation, and to hold them continuously in that state, nevertheless they may develop tumors of their own. In other words, the animal is resistant to outside agencies, namely, the extraneous cancer-cell, but not to processes taking place inside its own body.

Although all the foregoing facts are not disputed in the particular cases for which they have been described, the idea that cancer is infective still finds staunch supporters, even among experimenters themselves; notably Borrel, of the Pasteur Institute; Gaylord, of the New York State Laboratory; and, more recently, Klemperer [1] and C. Lewin, of the Berlin Charité Cancer Department. It must be admitted, however, that where they have sought to maintain their position, on the basis that the resistance which may be experimentally produced against the inoculation of cancer is like the immunity which may be induced against infective diseases, and due to antibodies, their contention has completely broken down, since they have not been able to adduce satisfactory positive results in support of their claims. Borrel, who originally inclined to the idea that the immunity reactions would clear up the nature of cancer—presumably the infective nature—later assumed the position that these reactions are all against the cancer-cell, and not against a cancer virus, and that they have little or no etiological value.

Apparent endemics of cancer in mice have been observed and explained as due to cage infection. Apolant,[2] in reviewing the evidence, writes: "In the first place the statistical data regarding cancer epidemics and cage infection are by no means generally recognized as of value. The occasional observation of accumulations of spontaneous tumors in mice and rats is not denied; I refer only to the communications of Borrel, Asher, Thorel, Gaylord, Kock, Loeb, Haaland. Since, however, similar occurrences have never been observed in the gigantic undertakings of Bashford and Ehrlich, it appears necessary to avoid drawing any far-reaching conclusions from the peculiar isolated observations which in part are also difficult to comprehend." Apolant goes on to review some of the most important instances of "endemics," including that of Thorel, which was proved at a later date to be possibly the consequence of a slow development of *inoculated* cancer cells!

Borrel, like Gaylord, has claimed alleged epidemics in labor-

[1] Klemperer, G.—"Der jetzigen Stand der Krebsforschung," Berl., 1912.

[2] Apolant, Hugo.—"Die experimentelle Erforschung der Geschwülste," Handbuch der pathogenen Micro-organismen. Herausgeben von Kolle und Wassermann. 1913. Bd. III, p. 220.

atory and other animals as evidence of infection. Other investigators, like Bashford and his colleagues, who have recorded the ages and ancestry of their own animals among whom cancer frequently appeared, declare that such concurrences are not epidemics at all, but the natural result of a high proportion of aged animals, possibly of the inbreeding of cancerous stock [1] and of exposure to certain specific parasites acting as irritants, for example, nematodes and cestodes in mice, or liver flukes in cows.

Borrel [2] first drew attention to the frequency of nematode infection in mice, and has relied upon the frequent presence of these organisms as evidence that they act as intermediate hosts for a cancer virus. Haaland [3] has described them in the connective tissue of the mamma of mice, where cancer so often arises, and has explained the frequency of chronic inflammation as caused by their secretions and excretions. Fibiger [4] also has employed nematodes in feeding experiments with rats, and in two or three cases carcinomata actually developed. Fibiger, however, did not incline to the above view, but rather to the opinion that the nematode had acted as an irritant. In this view he has been supported by Bashford [5] and others. It is remarkable that so very few true carcinomata developed in Fibiger's 2,000 rats.

Thus, while experiment has yielded no fresh evidence in favor of an infective etiology, it has not yet enabled those who hold to the purely cellular view to rout effectually their opponents. The latter, however, have been forced to abandon the idea of direct infection,[6] and to seek an explanation in a virus conveyed by an intermediate host, of whose existence, however, no direct evidence is forthcoming.

On the other hand, even where upholders of the cellular views have admitted that parasites play a part, they have found no difficulty in fitting this rôle into the conception that chronic irritation is the essential factor. With the exception of these investigators, and those, like Lazarus-Barlow, who seek to prove that all the irritants associated with cancer are radioactive,

[1] See remarks on *heredity* in Sec. III, p. 96 *et seq.*

[2] Borrell, A.—"Epithélioses infectieuses et epithélomas," Ann. de l'Inst. Pasteur, 1903, XVII, 81.

[3] Haaland.—Fourth Scientific Report, Imperial Cancer Research Fund, 1911.

[4] Fibiger, J.—"Ueber eine durch Nematoden (Spiroptera sp. n.) heroorgen ufere papillomatöse u. karzinomatöse Geschwülstbildung im magen der Ratte," *Berl. klin. Woch.*, 1913, p. 289; *Zeit. f. Krebsf.*, 1913, 13, 217.

[5] Bashford, E. F.—Nature, 1913.

[6] See remarks on goiter and "cancer" in trout in hatcheries, Sec. II, Chap. 2, p. 55 *et seq.*

the view is generally held that the irritants have no property in common beyond their association with cancer. Their intervention is not direct, but mediate. The common factor lies in the prolonged proliferation occurring under chronic irritation. Under this circumstance of prolonged proliferation, opportunity is given for cell variations, some of which are inimical to the rest of the cellular community of which the organism is composed.

When we leave the field of generalization for that of specialized work with the transplanted cancer-cell we enter a region where there is even greater disagreement. Some investigators hold that the study of the cancer-cell can teach nothing, that a virus has started cancerous growth, and is not, therefore, necessary for its continuation. Others assert that only by observing the transition from the normal to the cancerous cell is any evidence to be expected. Others again claim that the study of the transplanted cancer-cell has not taught anything which morbid anatomy and histology have not already clearly proved. Still others have steadfastly held that in studying the transplanted cancer-cell they are but imitating Darwin's study of the tame pigeon, with the application of his deductions to animals in a state of nature. The last school finds its chief exponents in the adherents of the Imperial Cancer Research Fund of London, who reason that the study of the transplanted or "tame" cancer-cell is bound to reveal some of its fundamental properties, arguing that its behavior during years of propagation must offer indications of what its possibilities were in its "wild" state, for example, in the animal in which it originally developed.

THEORETICAL RESULTS

Criticism of the Value of Propagation.—With regard to the value of the continuous propagation of the cancer-cell there has raged some acrimonious controversy, and it is only fair that a review of the criticisms of some eminent pathologists should be placed before the reader.

The earlier work appeared to offer many contradictions to human pathology. Notably, Ehrlich's tumors did not produce metastases, and growth was commonly found to be expansive rather than infiltrative. Von Hansemann vigorously attacked all experimental work as being based upon endothelioma, and not on carcinoma. All these objections have been overcome, and von Hansemann's arguments have been refuted by Apolant,[1] Bashford and Murray,[2] and Haaland.[3]

It is still too early to appraise properly the share played by experiment in the abandonment of certain views on cancer, and in the elevation of others to positions of prime importance as profitable working hypotheses. Opinions of representative pathologists are divided as to what has been accomplished in the past, and as to what may be accomplished by this means in the future toward advancing knowledge of the nature and etiology of cancer.

Adami,[4] an unbiased spectator so far as the interpretation of experiments is concerned, frankly ranks the evidence derived from experiments with that obtained from other sources. The enlightened outlook sometimes taken is illustrated by the following remarks by Ewing:[5] "No experimental evidence is needed to show that a malignant tumor may often be grafted from one part of the animal's own body to another, since the several recognized modes of metastasis daily demonstrate this process. Hahn, Cornil, and others have needlessly performed inoculations in human beings without contributing any important scientific information, while to-day such experiments are being successfully performed on animals for legitimate objects in many laboratories."

Although, as Ewing says, no experimental evidence is needed to show *merely* that a malignant new growth may often be grafted from one part of an animal's body to another, the fact that it can almost always be done experimentally illustrates the value of that method when applied to elicit exact information as to the relations obtaining between an animal and its own tumor. In short, such experiments have valuable bearings on every aspect of the highly important question as to whether a tumor contains anything foreign to the individual attacked; as well as on the part played in the inception of cancer by the relation between an organism and its tumor. This procedure is also valuable in testing immunity to inoculation, and in

[1] Apolant, Hugo.—"Die epithelialen Geschwülste der Mause." Arbeit. aus dem Kgl. Inst. f. experiment. Therap. zu Frankfurt a. M., 1906-8 (Parts 1-4), Pt. I, p. 1.

[2] Bashford and Murray.—"On the Genesis of Mouse Tumours." Second Scientific Report, Imperial Cancer Research Fund, 1905, No. 2, Part II, p. 15; "Carcinoma Mammæ in the Mouse," *Lancet*, 1907, Vol. I, p. 798.

[3] Haaland, M.—"Contribution to the Study of the Development of Sarcoma under Experimental Conditions." Third Scientific Report, Imperial Cancer Research Fund, 1908, p. 175; "Spontaneous Tumours in Mice." Fourth Scientific Report, Imperial Cancer Research Fund, 1911, p. 1.

[4] Adami.—"The Principles of Pathology," Chap. XV—The Neoplasms, London, 1909.

[5] Ewing, J.—"Cancer," Harvey Lectures, New York, 1908.

studying dissemination. From the standpoint of practical therapeutics it is the *sine qua non* for testing the value of alleged "cures." In many other ways the implantation of a tumor in the animal in which it arose has contributed and promises to contribute valuable knowledge.

The eminent German pathologist, Ribbert,[1] who has done so much toward demonstrating that tumors grow only from their own resources, and not by apposition through progressive transformation of surrounding tissue, is a hostile critic of the experimental method. He says: "Incidentally I might remark that in general the results which have been gained by extended experimentation on animals have been considerably overvalued, that is, if it was hoped to utilize them in explaining tumor genesis. Of the origin of tumors we have learned nothing that we did not know before. So far as the transplantability of tumors is concerned it should not surprise us in the least, only it could not be demonstrated so long as one tried to transfer human tumors to animals, for altero-transplantation is in general unsuccessful. Here, however, it is nothing else than a modified metastasis-formation."

Those who are familiar with the progress of knowledge on the difference in reactions obtaining when heterologous or homologous tissues are inoculated into animals will be struck by such a gloss of the reasons as to why efforts were ultimately concentrated upon the transference of cancer from one individual to another of the same species. The notion that cancer owes its inception to some common outside cause, led to all these attempts to transfer cancer from man to animals, or from an animal of one species to an animal of another species. It was the demonstration of blood relationship, as developed by the study of hemolysins and precipitins (as used to-day, for example, to discover if the blood stain found on a criminal's clothes is of animal or human origin), which led to the concentration of attempts to inoculate cancer by restricting such experiments to efforts on animals of the same species. Therefore it was not left for Ribbert to designate the artificial transference of cancer as a modified metastasis.

With the exception of a few authors, who have sought to use successful inoculation as proof of infection, or as being responsible for the spread of the disease, the implantation of cancers has always been recognized as artificial metastasis. However, Ribbert elsewhere confesses that with the microscope alone it is not easy to combat the assumption that a continually extending metamorphosis of neighboring cells, with consequent apposi-

[1] Ribbert, Hugo.—"Das Wesen der Krankheit," Bonn, 1909, pp. 48-49.

tional growth, occurs around malignant tumors. He says:[1] "I cannot disperse my opponents with histological evidence, be it ever so exact. We are not in a position to follow growth itself, but are reduced to the determination of isolated findings in dead material. Their significance is often not easily appreciable. What one thinks he has substantiated is reversed by another. It is just for this reason that I have brought forward theoretical considerations again . . ." Acknowledging that solely by the exposition of his microscopical findings he cannot succeed, Ribbert is obliged to fall back upon the results of recent experiment. This, by demonstrating that all the consequences of the local growth and dissemination of cancer may follow on multiplication, from their own resources, of a little group of cells implanted into a new host, has vindicated the justice of much that Ribbert has so ably sought to establish.

Ribbert[2] refers to the results of experiment as follows: "I may perhaps emphasize that investigation of the growth of animal tumors, particularly during transplantation, has led to the same result. This is of great significance, since such importance is ascribed nowadays to these experiments."

"The mention of experimental investigation impels me," he continues, "to discuss briefly a point which is able to support the conception that tumor-cells are not materially different from body-cells. In immunizing experiments one would naturally start from the assumption that the origin of immunity is a specific one, in a similar sense as with bacteria. However, Schöne, Michaelis, Borrel, and others have lately stated that one can also immunize with normal embryonal tissue.[3] From this fact it emerges that one need not use the cells of the tumor against which he wishes to produce immunity; that thus the normal elements already contain all that characterizes the tumor-cells, and that conversely these latter possess nothing which is not present in the normal cells. I have always thought so, and pointed out, upon a previous occasion,[4] that one might succeed in immunizing against carcinoma with normal epithelium, or perhaps with that of an atheroma."

Whether extension of a new growth ever occurs by apposition, and whether Ribbert is right in denying that a biological alteration takes place, transforming the normal cell into a cancer cell, are questions which cannot be settled by mere

[1] Ribbert—*Op. cit.*
[2] Ribbert—*Loc. cit.*
[3] The First to immunize with normal tissues were Bashford and Murray in 1906.
[4] Ribbert.—*Deutsch. med. Woch.*, 1906, No. 42.

microscopical examination. It may be recalled in this connection, that the view upheld by others before Ribbert embodies one of the most important facts as to the nature of cancer. Charles H. Moore,[1] as long ago as 1865, on the basis of his investigations at the Middlesex Hospital, London, and, later, his colleague, Campbell de Morgan,[2] held that cancer arises in a circumscribed area, and that growth or recurrence after operation results only from the cancer cells confined within this area. How much less satisfactorily this point is established by the theoretical method of Ribbert than by the application of experiment, must be evident to all who have read Ribbert's work. Especially is it unconvincing to those who have compared its results, as embodied in the foregoing quotations, with the simple fact of the experimental reproduction of the local and disseminated lesions of the disease after the implantation of a minute fragment of tumor.

Criticism of the Value of Prolonged Propagation.—So much for criticism as to the value of studying the manner and consequences of transference. When, however, the possible profit to be derived from studying cancer during prolonged propagation has come under criticism its usefulness is not admitted even grudgingly. Not only is it asserted that it has taught nothing, but it is declared that it cannot possibly teach anything. Even Orth, who is a supporter of the experimental investigation of cancer, and who has acknowledged its value, fails to see utility in studying the life-history of a tumor as prolonged by artificial propagation. "Not the study of transplanted cancer, but only the production of the causal genesis of cancer," is Orth's verdict in his latest available contributions.[3] Even where it appears probable that cancer has been produced experimentally, for example, by exposure to X-rays, or by feeding rats with cockroaches infected with nematodes, direct attacks have failed to elucidate the processes involved. It has never been denied by experimenters that the study of propagated cancer is only an indirect way of attacking the problems upon which Orth would make a direct attack; namely, through the relation obtaining between the reactive proliferation induced by chronic irritation and the development of can-

[1] Moore, Charles H.—"The Antecedents of Cancer," *Brit. Med. Jour.*, August 12 and 26, 1865, pp. 164 and 201, also p. 473.

[2] De Morgan, Campbell.—Discussion on Cancer, Trans. Path. Soc. of London, Vol. XXV, 1874, pp. 287 and 387.

[3] Orth, J.—"Ueber die Krebsgeschwülst des Menschen," *Sitzungsberichte der Kgl. pr. Akademie der Wissenschaften*, Jan. 28, 1909, p. 107; "Ueber einige Krebsfragen," *ibid.*, Dec., 1909, p. 1225; "Präcarcinomatöse Krankheiten und künstliche Krebse," *Zeitschr. für Krebsforschung*, Bd. X, 1910, p. 42.

cer. Thus the study of propagated cancer is regarded by some investigators as devoid of all etiological bearings, while others regard it as futile until more is known of the growth of spontaneous primary cancer. With regard to the first objection it may be stated that the results of the study of propagated cancer are already recognizable in many directions. For example, it affords no proof of a parasitic or infective etiology; it gives new reasons for delimiting the problem of origin as one peculiar to the individual from causes which are not constitutional, but local; [1] and it has defined the "age-incidence" of cancer as influencing inception, but not continued growth.

With regard to the second objection, it must be remembered that a study of the abnormal is often more practical than a study of the normal, and that, in the history of biological investigation, the study of the abnormal has frequently given the key to the solution of problems presented by normal processes. More than this, after exhaustive and inconclusive investigation of the normal, resort has been had to the deliberate production and investigation of the abnormal, as in the cases of the fertilization of the ovum; the elucidation of problems of embryology, regeneration, differentiation; and of the investigation of the parts played in heredity by the cytoplasm and nucleus of the cell.

The maintenance of the idea that only the production of primary cancer at will can carry us further in the investigation of the causal genesis of cancer, is one presentation of an attitude adopted from time to time during many years by eminent morbid-anatomists. They have not succeeded, however, in producing cancer and in describing the process, and it is therefore strange that they should not appreciate the value of emancipation—even if only for a time—from the restrictions imposed by the study of cancer at its site of origin, and by the material provided by the operating theater and autopsies. They appear equally inappreciative of the value of freedom from the limitations imposed by a study of what a cancer is at the time it is found, without clear evidence of what stages had preceded it, or through which it had already passed, and without evidence of any kind as to what all the future potentialities of cancerous growth might be.

The experimenters themselves, however, have pointed out and had acknowledged from the first that they claimed to do no more than study the ready-made cancer-cell for prolonged pe-

[1] See Introduction, Fourth Scientific Report, Imperial Cancer Research Fund, 1911.

riods of time, under altered environment. They have persistently correlated their study of propagated cancer with the study of the disease as it develops naturally in man and animals. They have been studying "the pathology of the living," as Moynihan expresses it, for man, and some of them claim that they have seen the development of new tumors from the material they have propagated.

The comparative knowledge acquired has made it evident that the negative results of attempts to *produce* cancer in animals are to be explained by the fact that this was attempted, perhaps quite irrationally, by subjecting the animals to various agencies reasonably held to be associated with the development of cancer in *man*. It early became evident, for example, that chronic irritants having a relation to cancer did not act by virtue of a common factor. Indeed, although to-day it is known how manifold and different are the irritants having relation to cancer in man (apart from certain physical injuries and the less definite evidence of the mediate intervention of some parasites), little is known of the extent to which irritants may be responsible for cancer in animals. However, the frequency of cancer on the surface of the body of vertebrates living in a state of nature is suggestive in this connection. At the same time, the remarkable divergencies in the liability of a single organ to cancer, for example, the mamma and the liver in mammalia, have acquired enhanced significance, since they show that factors other than the mere intervention of irritation, with its prolonged sequelæ, are operative. Such divergencies in the incidence of cancer in organs common to the mammalia [1] point to the possible importance of peculiar idiosyncrasies of species, and, in so far as irritants or parasites play an intermediate rôle, it follows that those effective for one species may not be effective for any other. Claims have been made that cancer has been produced experimentally in rats; for example, sarcoma at the root of the tail after exposure to X-rays (Clunet, of Paris), and carcinoma of the stomach (Fibiger, of Copenhagen).

Sarcoma is at present a risky field, owing to the many gradations to granulomata of unknown or uncertain etiology, and in the Fibiger experiments the remarkable fact that so few cases of carcinoma developed must be brought into relation with the circumstance that we do not have control of the frequency of carcinoma of the stomach for rats under other conditions, for example, such as the hereditary influence which has been proved to act in mice.

[1] See Zoölogical Distribution, Section II, Chapter 2.

THE BEARING OF IMMUNITY REACTIONS AND OF PROPAGATION ON THE NATURE OF CANCER

When the general results of recent research are left, in order to consider the highly specialized investigations of the phenomena of growth and immunity, it is difficult to present a short review of the enormous mass of literature which has rapidly accumulated in the past twelve years. An excellent review of practically all that has been done has been made by Woglom,[1] of the Crocker Cancer Fund of Columbia University, New York City. This author, however, unfortunately refrains from weighing up the evidence in favor of this or that conclusion, except in an all too short final chapter. He gives, however, a very valuable bibliography and a most excellent index to all details.

During many annual visits to Europe I have had opportunities of becoming familiar with the details of the investigations of the Imperial Cancer Research Fund in London, and of studying the painstaking scientific work which has been carried on by the staff of that institution.

It is perhaps unfortunate that the adequate investigation of cancer on an experimental basis requires such enormous resources in money, in men, and in animal material. These resources have been available, in practically only two centers in the world—to Ehrlich, of Frankfort-on-Main, and to Bashford, in London. In the scope and magnitude of his investigations Bashford has been enabled to outstrip his teacher, Ehrlich. In all essential records of fact, teacher and pupil are in agreement, but as would naturally be expected from men who by nature are determined to cut out paths of their own in any wilderness, even that of cancer, there are divergencies of interpretation to which reference will be made.

In view, therefore, of the unique and extensive experience of Bashford, who, as the Director of the Imperial Cancer Research Fund, has had at his disposal a material greater than that commanded by any other investigator, it has seemed expedient, for the details of the particular subject now under discussion, to rely mainly upon the summaries which he formulated for the International Medical Congress held in London in 1913, more especially since they met with no criticism invalidating any single statement of fact. In other paragraphs the divergencies of these views from those of Ehrlich will be

[1] Woglom, W. H.—"The Study of Experimental Cancer," Columbia University Press, 1913.

summarized on the basis of the latest publication from his Institute. The text has been paraphrased in order to avoid technicalities which are not commensurate with the scope of the present volume. The reader who is interested will find them described in detail, and well indexed, in Woglom's excellent monograph and in Apolant's article in the well-known encyclopedia of Kolle and Wassermann.

The Constancy and Variability of Tumor Cells.—In no laboratory has the propagation of cancer been undertaken upon the scale adopted at the Imperial Cancer Research Fund, where as many as 86 mouse-tumors of different primary origin were kept in propagation for a long time for the purpose of studying their relative constancy and variability. In many cases these tumors were growing also in several parallel sub-strains. This enormous material has given unrivaled opportunities for the comparative study of the biology of the tumor-cells of the mouse. In addition, tumors of the rat, rabbit, guinea-pig and dog (for three generations only) have been successfully cultivated for the sake of the general application of the facts to mammalia in general. Ehrlich's is the only other institution which has kept going a large number of strains restricted to the mouse and rat. At one time Ehrlich had as many as 10 strains of mouse tumors of different origin. These, however, were only a fraction of the number grown in London, and they had not the greatly varied character found in Bashford's laboratory. Therefore, while permitting of some conclusions of great importance, Ehrlich's views have met with contradiction from other laboratories. On the basis of the experience of the Imperial Cancer Research workers they have been found to be subject to limitations, and some of the essential facts observed by Ehrlich have been shown to be capable of other and more valid interpretations.

Constancy and Variability of Histological Structures.—Evidence of the tenacity with which the same structure may be retained is furnished by a tumor which, after eight years and 71 sub-transplantations, retained in two separate strains the structure of the original primary growth, namely, a papilliferous adenoma. Two other tumors of similar structure, after growing for seven and five years respectively, still retained the original structure. On the other hand, a fourth tumor, which in earlier transplantations was very gland-like, presented later a solid structure. Other tumors exhibiting a solid structure at the beginning of propagation, continued to do so.

One particular tumor, which caused the development of sarcoma (see below), because of the extreme variability which it showed was propagated for about three years in as many as 17 separate parallel series. Later seven of these parallel series were maintained in growth for another two years. The structure of the several carcinomatous and sarcomatous strains, although differing markedly one from another, yet remained quite constant in each strain: (a) alveolar carcinoma; (b) three strains of adenocarcinoma; (c) one strain of carcinoma with spindle-shaped cells; (d) polymorphous-celled sarcoma; and (e) spindle-celled sarcoma.

Six tumors were propagated which showed keratinization as the typical differentiation of the primary growth. Two of them continued to produce typical squamous epithelium after two and three years' growth, and 31 and 33 transplantations, respectively. A third, in which keratinization was combined with the formation of sebaceous material, continued to do so after three years and 27 sub-transplantations. The other three completely lost the power of keratinization after varying lengths of propagation.

Of tumors showing sebaceous differentiation, two maintained this character in full, one for four years, during 29 sub-transplantations. The third showed sebaceous differentiation regularly for the first 30 transplantations. In the succeeding six transplantations this change was usually absent, and when present was only small in amount, the tendency to sebaceous differentiation apparently disappearing completely. The fourth showed sebaceous material and keratin in the original primary tumor. The keratin continued in one strain for seven transplantations, then disappeared, to reappear again slightly from the nineteenth to the twenty-fifth transplantation. In the fortieth transplantation it was found that the vacuoles contained, not sebaceous material, but glycogen. This must have been going on for some time, the glycogen being mistaken for fat. Another strain showed keratin and a small amount of sebaceous material continuously for 20 transplantations, when both were lost and had not reappeared throughout another 20 transplantations.

Relatively enormous quantities of glycogen continued to be formed by a tumor which was propagated for five and one-half years. On the other hand, a tumor which showed considerable amounts of glycogen in the earlier transplantations did not fully retain this character. The glycogen became gradually less in amount during six transplantations, and almost disappeared.

Constancy and Variability of More Subtle Properties.—While keratin, glycogen, and fat formation are biochemical activities of the cancer-cell capable of microscopical study, there are others which cannot yet be made evident to the eye, except in their consequences. Such are, particularly (1) the power possessed by some rare carcinomata of producing sarcoma in the connective tissue of healthy mice, and (2) the conditions known as immunity reactions, referred to below.

Sarcoma Development.—The remarkable phenomenon was first described by Ehrlich and Apolant.[1] The process has since been observed in other laboratories. It consists essentially in a transformation of the stroma into sarcoma because of some hitherto undefined influence proceeding from the carcinoma cells. Ehrlich and Apolant assumed that the end of all carcinomatous tumors during propagation would be their replacement by sarcoma. Therefore the loss of power to induce sarcoma is of great theoretical interest.

The loss of the power to effect a sarcomatous transformation of the connective tissues occurred in five carcinomatous sub-strains derived from a strain which called forth sarcoma development irregularly, and its appearance was promoted rather than hindered by rapid repetition of the transplantations. Another tumor caused the development of sarcoma in practically every animal, from the twelfth to the twenty-fifth transplantation, in all the sub-strains propagated, if the tumor was permitted to grow for about two months; but remained pure carcinoma if transplanted at intervals of a month or less. Four carcinomatous sub-strains which were kept growing presented variations from this behavior.

In the first sub-strain the variation was in the direction of an earlier appearance of the sarcoma. This occurred after the twenty-fifth, and continued during the next twenty transplantations, until, finally, the early onset of sarcoma development, combined with slow growth of the carcinoma proper, rendered it impossible to retain the carcinoma in propagation, and the strain became pure sarcoma. In the second sub-strain the change began to appear at a later period, occurring only after one hundred days or more, instead of after sixty days. Subsequently, even after two hundred days, the tumors remained pure carcinoma. This condition continued during fourteen transplantations, or fifteen months, and the power of producing sarcoma was ultimately lost. Sub-strains 3 and 4 began by causing sarcoma about the sixtieth or seventieth day, continuing to do so up to the fifty-third transplantation, but thereafter the appearance of sarcoma was delayed, so that the complete loss of this power seemed probable.

[1] Ehrlich and Apolant.—"Beobachtungen über maligne mäusetumoren," *Berl. klin. Woch.*, 1905, 28, 871.

The power to induce sarcoma development is characteristic of only a small minority of transplantable tumors. When it occurs it is almost certain that it is a characteristic of the primary tumor. The same phenomena have been observed in transplantations of spontaneous tumors into the mice from which the primary tumors were obtained. This condition has also been demonstrated in man.

At the Rockefeller Institute growths in the fowl have been discovered which, under the microscope, it is impossible to distinguish from sarcoma, and which are transmissible by means of a virus contained in a cell-free filtrate obtained through a porcelain filter and by a dried powder. Cell-free filtrates prepared from carcinomatous tumor, and tumor of mixed carcinomatous and sarcomatous structure, as well as pure sarcoma of the mouse, did not lead to tumor formation after inoculation. It has been impossible, therefore, to separate the property of producing sarcoma from the vital activity of mouse tumor cells. The same negative results followed the inoculation of these tumors when dried *in vacuo*. The differences between the "sarcoma" of the fowl and the mouse in these respects are not fully cleared up, and the sarcomatous nature of the fowl tumor is received with skepticism by some authorities. The nature of this activity of some mouse carcinomata is still as obscure as that of the origin of malignant new growths in general. The attempt to explain sarcoma development by the transference of a virus from the carcinoma cell to the connective tissue is unsatisfactory, since it will not explain the subsequent loss of this property and at the same time the continued growth of the carcinoma cells.

The Immunity Reactions.—The employment of the term "immunity" with reference to cancer signifies nothing more than the exemption of the individual—under clearly defined circumstances—from the consequences of transplanting a tumor from another individual of the same species.

Resistance to the transplantation of cancer includes a large number of phenomena which are of the nature of hindrances to the continued growth of the already fully developed cancer-cell. The analysis of these phenomena has permitted the discovery of some subtle properties of the cancer-cell, as well as of some of the relations existing between it and the animal in which it grows, both in the case of the natural and in that of the transplanted cancer-cell.

Artificially induced resistance to the continued growth of grafts does not create any exemption from the liability to the development of cancer. It is certain, too, that cancer is rarely, if ever, communicated naturally or spontaneously from one individual to another by transplantation, and that its great frequency cannot be explained in this way. Therefore the mechanism of its natural development differs fundamentally from transplantation, and the use of the term "immunity" may be justified only by convenience.

The study of such artificial resistance, however, has thrown light upon the nature of the tumor-cells and their relation to the individual serving as food purveyor. But sharp distinctions must be drawn between heterologous, homologous, and autologous[1] inoculations, whether employed for the purpose of inducing or of testing resistance.

Resistance to Heterologous Inoculation.—Heterologous inoculation may be practiced in two ways. One species of animal, say a rat, may be inoculated with the tumor of another animal, say a mouse, and the rat may then be tested as to resistance to an inoculation of its own kind of tumor, or for resistance to mouse tumor. In the first instance no resistance is induced; in the second there is.

There is general agreement that the normal tissue of tumors of one species of animal is incapable of progressive growth, or even of continued existence, in another species. Very extensive investigations have been made into this subject, and the few positive results cannot be set up against the enormous preponderance of negative results obtained. By far the greater mass of accumulated data shows that tumors of one species are incapable both of progressive growth in another species and of power to induce resistance to tumors of the species inoculated. These two lines of inquiry, therefore, agree in bringing out general exemptions which can be explained only on the basis that tumors have a specificity analogous to that distinguishing the organisms from one another as zoölogical species. Of themselves these two groups of phenomena have no bearing upon the resistance which may be induced against the inoculation of tumors into other individuals of the same species. In conjunction with other studies they do have a bearing upon the question of whether an immunity is induced analogous to that against infective diseases, by showing that, when induced, it does not depend on a virus common to cancer in whatever species of animal it occurs.

Induced resistance to a repetition of the heterologous inocu-

[1] Heterologous inoculation = from one species to another.
Homologous " = from one animal into another of the same species.
Autologous " = reinoculation into the same individual.

lation has been demonstrated to occur and to give reactions identical in nature, both *in vivo* and *in vitro,* to the well known hemolytic and cytotoxic reactions induced by immunizing with antigens from strange species. It is possible that the tumors and tissues of nearly related species—for example, the blood of the rat and of the mouse—do have a slight reciprocal influence; but, if so, its existence only serves to emphasize the importance of blood-relationship rather than the intervention of a cancer parasite common to the different zoölogical species.

The tissues need not be alive in order to induce the hemolytic, cytolytic, and heterologous cancer immune reactions, but retain this power, for example, after mechanical disintegration.

Heterologous Immune Sera.—One of the hopes awakened by the knowledge of the cytotoxins was that of a further development of a rational organotherapy. In the promotion of more accurate diagnosis, and in forensic medicine, the methods relied on have yielded advances of prime importance; but the hope of fresh therapeutic triumphs has not been fulfilled. The sharp specific distinctions which at times may be drawn *in vitro* between normal and cancer-immune sera do not necessarily obtain also *in vivo.* In the test-tube they present, in varying degree, hemolytic precipitin and cytolytic reactions which as yet have not been shown to have any distinctive characters. "Cancer-immune" sera must to-day be regarded as devoid of all action in the living body. As vehicles for the communication of passive immunity, such heterologous sera have proved valueless, and likewise they have not been demonstrated to possess qualities which may be relied upon for purposes of diagnosis.

Under this category it is convenient to refer to the results which have been interpreted as toxic or anaphylactic phenomena following a repetition of an inoculation. On the basis of careful and numerous repetitions of the method on which such observations have been advanced, the conclusion has been reached that they are due, not to anything specific to cancer tissue, but rather to accidental bacterial contamination.

Homologous Immunization and Resistance.—Homologous resistance may be considered from the standpoint of whether it is preëxistent and natural or induced by active changes following various procedures.

Natural Resistance.—Natural resistance played a much more prominent part at the beginning of the investigation of immunity to cancer than it does to-day. During the period when an appropriate technic was being developed, many observations could not be otherwise than tentative. For example, with one form of technic the primary transplantation of certain hemorrhagic mammary growths of mice succeeded not more than once in 500 attempts. With a different technic these growths were as easy to transplant as other mammary tumors. Naturally the appearance of 499 resistant mice out of 500 was calculated to give great importance to natural resistance. The real explanation, however, was found in the employment of such large doses for inoculation that auto-immunization was induced and growth stopped. Perhaps also the greater suitability for growth of young than of old mice was not fully recognized at that time. The existence of a certain amount of natural variability in power of reaction in different animals cannot be denied, and account must also be taken of age, site, dose, and time interval. Although some tumor-strains are relatively indifferent to age, no strain has been found which grows better in old than in young animals. Young animals, as a rule, are more susceptible than old ones, whether they come of normal or of cancerous stock, the latter not offering a more favorable soil.

Since young animals are more suitable for inoculation and continued growth than old animals, the rarity of cancer in the young is not due to constitutional resistance to growth, and its frequency in the old is not due to a constitutional change, occurring with senescence, favorable to the growth of cancer in general. This conclusion suggested experiments to determine whether animals naturally suffering from the disease offered a more suitable soil than others for the growth of cancer in general. It was found that they did not do so. Whereas the re-inoculation of an animal with its own tumor is almost always successful, the success of the primary transplantation on inoculating other cancer-animals is on a level with that for normal animals. The strict individuality of spontaneous tumors has been demonstrated by the resistance which the majority of strange hosts offer to the introduced cancer-cell, and by the fact that it is impossible to immunize a mouse against an inoculation of its own tumor.

Active Resistance Induced by Tumors.—Active resistance may be induced in a variety of ways—by inoculating with spontaneous or propagated tumor without obvious growth following; by inoculation with propagated tumors which, after a considerable amount of transitory growth, become absorbed; or by inoculating with normal tissues.

If the dose of spontaneous tumor inoculated without giving rise to daughter-tumors in normal mice has been sufficiently large, they will exhibit resistance to a second inoculation of a propagated tumor which takes in maximum percentage and possesses extreme power of growth. The extent of the resistance is not uniform for all such negative inoculations with spontaneous or propagated tumors. If the dose be too small resistance may be practically absent, and the animals may react almost normally by giving a number of tumors approximating to the control. Conversely, the dose used to test the existence of resistance, if present, may be so large as to overcome it. Spontaneous tumors also vary among themselves in the extent to which they induce resistance against the same test tumor-strain.

Propagated tumors exhibiting the phenomenon of transitory growth followed by spontaneous healing, induce resistance to reinoculation whenever this results. This resistance is usually absolute for a secondary inoculation of the same tumor-strain, but may be only partial or altogether absent in the case of different tumor-strains. There is, thus, a degree of resistance common to all tumors.

Active Resistance Induced by Normal Tissue.—Normal tissues—defibrinated blood, erythrocytes, liver, spleen, testis, mammary gland, kidney, placenta (freed from blood), entire embryos, embryonic skin, etc.—induce a high degree of resistance. The most convenient tissues with which to work are blood and embryonic skin. The latter is especially suitable, because of the great uniformity that may be obtained, both technically and in the results, and because it is also the most potent. Spleen, while giving a high degree of resistance, is apt to be infected. Liver is also liable to be infected, and is not so good an immunizing agent. Serum and plasma do not induce any resistance. The dosage of normal tissues can be more accurately adjusted because of the uniformity of the material and of the amount of growth exhibited on transplantation—a variable factor which may be excluded in the case of blood.

The power to induce resistance varies from one tissue to another, and the same tissue does not induce the same degree of resistance against all tumor-strains. The blood produces a high degree of resistance against one strain, but not against others. Embryonic skin was found to produce the highest degree of resistance against a squamous-celled carcinoma. This gave rise to the surmise that histological relationship might have some specific influence, although the possible influence of a high and pure dose of epithelium could not be excluded. Further experience has not yet tended to confirm this view as to histological relationship, and the results may be explicable rather by the varying qualities of the tumor-strains, rendering some more susceptible to resistance, as described below.

The high degree of resistance induced by spleen is remarkable, and has attracted particular attention, owing to the apparent rarity of metastases in this organ. Testis was stated not to produce resistance, but has also been found to do so.

The Parallel in the Onset, Duration, and Distribution of the Resistance Induced by Tumor and Normal Tissue.—After an immunizing inoculation the parallel in the rise, duration, and disappearance of immunity induced by normal and tumor tissue, as shown in the accompanying curve (Fig. 1), is of great

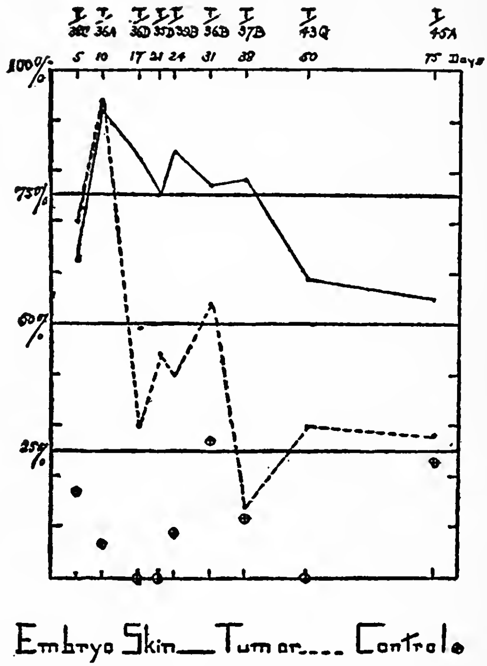

FIG. 1.—*Curves showing the extent and duration of the resistance induced in mice with embryo mouse skin and spontaneous adenocarcinomata of the mammary gland of the mouse, respectively. The percentage of immune animals is depicted on the vertical, the duration of immunity on the horizontal.

importance. Of normal tissues skin always induces a higher, and kidney a lower level of resistance than does spontaneous tumor. There is throughout, however, a parallel course for all three curves, the maximum being attained at about ten days, with a return to the normal level after about eighty days. This parallel of itself would serve as evidence that resistance is identical in nature, whether induced by normal or cancer tissue. An extraneous agent or virus cannot be made responsible for the resistance induced by embryonic skin, and there seems no

* From Woglom, in *Journal of Experimental Medicine,* Vol. XVI, No. 5, 1912.

reason to suppose that the resistance induced by cancer tissue is due to any property other than that of cancer *qua* mouse tissue.

The resistance conferred by an immunizing inoculation is distributed all over the subcutaneous tissues of the body, the peritoneum, and the internal organs (kidney), extending even to the blood. If a tumor-strain naturally giving rise to metastases be injected as fine emulsion into the tail vein, metastases in the lungs can be stimulated, but in immunized animals the number falls far behind that of the control. The wide distribution of resistance throughout the body almost makes the assumption of the presence of some substance in the body-fluids a necessary postulate, and the indications of quantitative relations point in the same direction.

Distinction Between Living and Dead Tissues.—Both tumor and normal tissue must be alive in order to call forth resistance. If killed, or disintegrated so that no intact cells remain, no resistance is induced. This applies whether the means employed be chemical, mechanical (as effective crushing at or below 0° C.), or actinic (as heat or exposure to radium). The absence of immunizing effect cannot be overcome by enormously increasing the dose. Even red blood corpuscles, if completely ground at the temperature of ice and salt, lose all power to induce resistance. It would appear that growth following inoculation must contribute to the production of resistance by actually increasing the dose of the effective substances; yet mere growth of itself seems to be non-essential, since growth of the inoculated red blood corpuscles may certainly be excluded. Some subtle product of metabolism of the living cell, in consequence of whose action a change is effected in the body-fluids of the resistant animal, appears to be essential.

Homologous Immune Serum.—The serum of immunized animals has not yet been shown in *in vitro* experiments to differ from that of normal mice, nothing of an antitoxic or cytolytic reaction having been discovered. Neither has it been shown to possess curative powers, nor has passive resistance been conferred by its means. The milk of highly immune mothers conveys no resistance to their offspring.

Nature of the Change.—The nature of the change effected by immunizing has been elucidated in part by studying the processes of the spontaneous healing of tumors; by examining the site of grafting in normal and in immune animals; by searching for histological evidences of reaction throughout the body; by analyzing the results of double inoculations of different tumor-strains; by observing the effects of the progressive and transitory growth of tumors on the relative weights of the several organs of the body; and, lastly, by observing any changes which may occur in the metabolism.

Spontaneous Healing.[1]—The phenomenon of spontaneous healing may be obtained with any desired frequency from a sufficiently representative series of different propagated tumor-strains. It is extremely rare, however, in spontaneous growths, not occurring as often as once in every hundred of the spontaneous tumors observed.

Very characteristic histological pictures of tumors undergoing absorption, after growing for a time, and perhaps attaining huge dimensions, have been described by Bashford and Murray, Cramer, and Gaylord. There are hemorrhages; the tumor-cells vary in their staining capacity, exhibiting light and dark areas, or they are more obviously degenerating; aggregations of plasma-cells are more frequent than in growing tumors; later the tumor-cells are cut up into groups surrounded by a large zone of phagocytes, and ultimately scar-tissue forms.

The conditions obtaining between the connective tissue and the cancer-cells are obviously quite the opposite of those existing in a growing tumor. From the histological investigation the primary change appears to arise in the tumor-cells themselves. While this cannot be determined by direct microscopical observation, it is shown to be the case by the fact that, while one tumor goes on growing, another, in the same host, is being absorbed. That the primary change is in the tumor-cells has been determined by studying the site of inoculation in normal and in immune animals, and by investigating the resistance which tumors induce against themselves, as described below under auto-immunization. The histological appearances are exactly analogous in the rare phenomenon of the healing of spontaneous tumors, and in their case also changes in the tumor-cells themselves play the determining rôle. As in transplanted tumors, one spontaneous tumor may be absorbed while another continues to grow. Whether or not constitutional hindrances to growth also develop, as in transplanted tumors, has not yet been determined.

Examination of the Site of Grafting.—When a minute graft is made into a new host the carcinoma-cells persist and grow progressively. The supporting scaffolding of blood vessels and connective tissue degenerates and is supplied afresh by the new host reacting to the chemotactic powers of the cancer-cells in such a specific manner that the structure of the mother-tissue is exactly reproduced, perhaps after years of continued propaga-

[1] See General Bibliography.

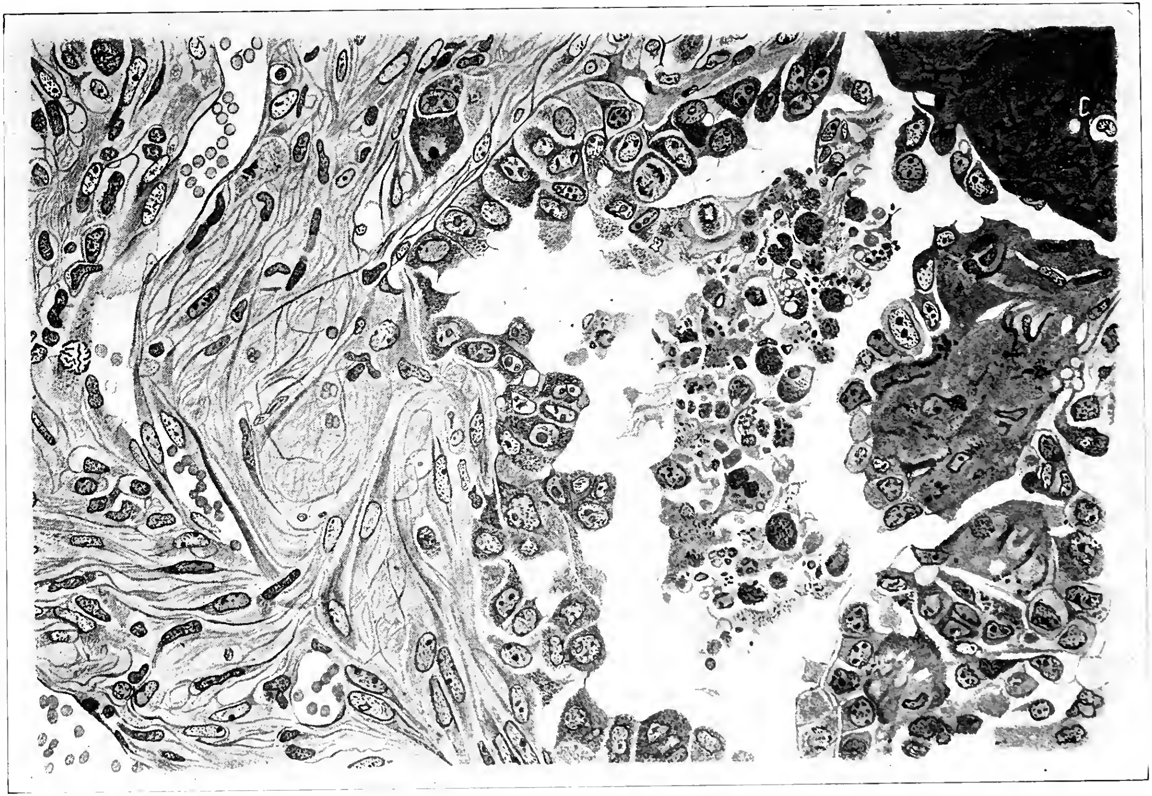

Plate XXXVI.—High power view of failure to supply the specific scaffolding on the part of an immunized rat. (Woglom, Fifth Scientific Report, Imperial Cancer Research Fund, 1912.)

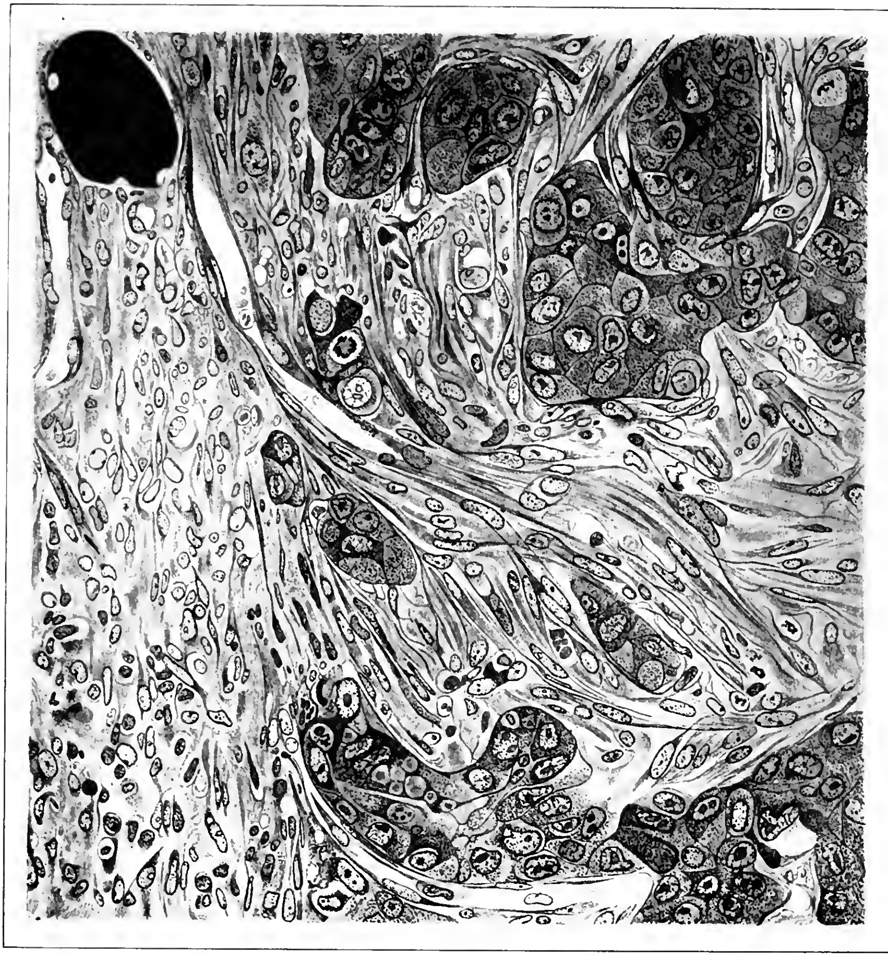

PLATE XXXVII.—High power view of the formation of new blood-vessel and stroma scaffolding for a graft of carcinoma in a normal rat. (From Woglom, Fifth Scientific Report, Imperial Cancer Research Fund, 1912.)

tion. In animals immunized by normal or tumor tissue this *specific* reaction does not take place. Superficial examination may lead to the conclusion that the reaction is the same, but the careful examination of serial sections shows that neither the connective tissue nor the blood-vessels of the immune host penetrate the graft in the same way as in normal animals. There is a reaction in immune animals, but it is of a different nature. In the immune animal the cancer-cells are lying in a single layer against a solid wall of the host's tissues at a time when in a normal one the graft would be developing into a well-recognized miniature tumor. They are as near the food supply as they can get, and are not immediately or directly killed by some potent cell-poison. Their architectural powers of molding a new stroma of blood-vessels and connective tissues from the host appear to be paralyzed, and ultimately they are so injured as to die or to succumb to the formation of scar-tissue. The process is essentially the same as in spontaneous healing. It is more acute because the immunity reaction was existent before the graft was introduced, whereas in spontaneous healing it is induced concomitantly with the growth of the tumor which it must overtake.

It is possible to proceed further by applying the information thus gained to an analysis of the difference obtaining when inoculation is successful, and when it fails in animals already bearing tumors. The method now employed is to inoculate two tumor-strains, either simultaneously or at intervals one after the other, and then to examine the site of the graft. The same histological differences described above are again found between the two cases, and the same mechanism of active resistance may be inferred.

Reaction Throughout the Body.—Apart from the fact that resistance is disseminated throughout the body, it has been found that the connective tissue contains an excess of plasma-cells during the time when the resistance is developing.

The Relative Weights of the Several Organs.—The growth of a tumor hinders the growth of the animal bearing it, so that very young animals may remain dwarfs as compared with others of the same age that have remained free from tumors. When the several organs of tumor-bearing animals are weighed and expressed as ratios of the total body-weight (minus tumor), it is found that there is a relative hypertrophy as compared with the normal. Thus hypertrophy is most marked for the heart, lungs, liver and kidney, and spleen. Owing to the great fluctuations occurring in the weight of the spleen from other causes, the interpretation of the figures for this organ must be made with caution.

From the standpoint of immunity it is of importance to determine whether this hypertrophy is due to supplying the needs of the tumor, or whether it is concerned in the development of resistance. In this connection the heart, lungs, and kidney need not be considered. The spleen is particularly interesting, owing to the apparent rarity of metastases in it. The prominent part played by the liver in dealing with all intoxications also claims attention for this organ. It is necessary to consider the effects produced by tumors which always induce resistance and strains which never do so. The ratio of the weight of the spleen to the body-weight varies in normal animals from 1:54.4 to 1:81.4, the body-weight being reckoned after removal of the alimentary canal plus contents. Similarly the liver varies from 1:12 to 1:14.4. The hypertrophy of the liver and spleen is greater in animals bearing progressively growing tumors than it is in animals in which tumors are undergoing absorption or have already been absorbed. It follows, therefore, that the hypertrophy of the liver and spleen occurs independently of the influences proceeding from a tumor and calling forth active auto-immunization. The hypertrophy is concerned in promoting growth, and not in hindering it. The tissue of the hypertrophied organs (liver) has undergone no modification in its immunizing property.

Auto- or Concomitant Resistance.—From the preceding results it has been possible to advance yet deeper into the biological properties of the cancer-cell, and to determine the nature of the difference between tumors growing progressively and those exhibiting only transitory growth.

The behavior, on transplantation, of propagated tumor-strains differs greatly. In a representative series of eighty-six strains of different primary origin there are, at one end, strains which take in 100 per cent. of all animals, which grow rapidly and always progressively, and which, under suitable conditions, exhibit metastases in a high proportion. At the other end there are strains which, although they take in 100 per cent., grow only transitorily and all become absorbed. Between these extremes there are series exhibiting all possible combinations of rates of growth, proportions of takes, and of absorptions.

The reason for the difference is to be found chiefly in the varying degrees to which the tumor-cells are able to elicit an active reaction against themselves, and in which they are susceptible to it. The susceptibility of the animal plays a minor part. Although, theoretically, natural resistance cannot be altogether dismissed, practically it may be left out of account, and the conception of variability in power of reaction from animal to animal substituted for it. There are tumor-strains which induce a powerful auto-immunity or concomitant immunity in every animal which, within limits, is more rapidly effective and of higher degree the larger the dose. There are strains which induce no such reaction whatsoever, so that an increase of dose merely leads to larger tumors in a shorter time. Between these two groups there are all gradations.

The effect of the primary inoculation on a secondary inoculation is the same, whether the latter be practiced with the primary tumors present or after their surgical removal. According to the nature of the tumor first inoculated there will be, respectively, no resistance, or an active resistance, to the secondary inoculation. In the latter case the examination of the site of the secondary inoculation shows changes identical with those found upon examination of early grafts from animals which have been actively immunized by normal or tumor tissue, namely, absence of the *specific* blood, vascular and connective tissue scaffolding on the part of the host.

Autologous Inoculations.—With reference to their reactions to tumors other than their own it has been determined that mice with primary tumors present no deviation from normal mice, either as regards suitability for inoculation or for immunization. All methods of immunization are powerless against the reinoculation of their own tumors. While resistance is effectively present against a strange tumor, an autologous inoculation will always overcome it if, indeed, any resistance is offered, of which there is no evidence. Conversely an inoculation of an animal's own tissues is equally incapable of protecting it against the growth of a tumor from another individual.

Since an animal's own normal tissues do not induce resistance to an homologous cancer inoculation, there is no reason why its own cancer tissue should do so, and tumor-cells, upon autologous inoculation into immunized animals naturally subject to cancer, probably do not even require to overcome the homologous resistance. The tumor-cells are indifferent to the existence of resistance when replaced in their natural host.

Loss of Power to Induce Resistance and Acquisition of Powers of Continuous Growth.—Tumor-strains which, although taking in a high percentage of cases, exhibit only transitory growth and produce active resistance, present exactly the same features as do normal tissues on transplantation. There is the difference, of course, that, although normal tissue cannot be grown in an indefinite succession of hosts, such tumors can be, if transplantation is performed sufficiently early. Of great importance is the observation that from mother-strains exhibiting these phenomena there may be obtained daughter-strains with better powers of growth—which are even possessed of progressive growth—in every animal, and which are able to produce metastases in a high percentage of animals. Such altered daughter-strains have not become insusceptible to the immune reaction or "serum-fest." As grafts they remain susceptible to resistance induced by normal tissue or tumor, but they have lost the power to induce resistance to their own growth and to the growth of other tumors.

This change must be of great, indeed of fundamental importance, since an animal 200 to 400 times the weight of the dose of cells can be rendered absolutely resistant, and an evident resistance is produced even if the dose be only 1/3000 of the weight of the animal; but after the change the power to induce resistance is lost entirely, for evidence of its retention, even in reduced degree, has not been obtained by increasing the dose. The changed cells no longer induce hindrance either to their own growth or to the growth of other tumors. In this respect, therefore, they behave in normal animals in the same way as autologous inoculations of spontaneous tumor. It would appear that a new fact bearing on the correlation of growth has been brought to light by showing how progressive powers of growth have been acquired in the case of such daughter-tumors.

Hypersensitiveness.—The use of the term "hypersensitiveness," as of "immunity," may be justified only by convenience. The condition has nothing in common with anaphylaxis, and merely implies an alteration in the soil, in consequence of which tumors grow better.

The phenomenon has been described after the inoculation of tumor tissue or normal tissue, either undamaged or treated in various ways, as by heat or crushing. It is not an antecedent stage in the production of resistance, but rather a later phenomenon. The subject is not thoroughly cleared up. Apparently it is of the nature of a neutralization of the power to react with active resistance, and not a persistent stimulus to growth. It has not yet been found possible to obtain clear evidence of the abolition of immunity by inoculating crushed material into an actively resistant animal.

Possibility of Applying Results to Explain Nature of Cancer.—Active resistance is effective against grafts and emboli, and hardly effective, or not effective at all, against well-established tumors, except such as are liable to spontaneous healing in consequence of auto-immunization. A slight effect of active resistance, never amounting to cure or persistent holding up of growth, can be obtained on strains which do not induce auto-immunity, and which grow progressively in consequence.

A problem of great interest centers in the difference between the great susceptibility of grafts to active resistance and the relative or absolute insusceptibility of established tumors. This contradiction is of primary importance in any discussion of the nature of cancer immunity. It has not yet been completely resolved, but the conclusion has been drawn that something circulating in the fluids and acting on the cancer-cells is responsible for the histological pictures observed (1) for grafts and emboli in immunized animals, (2) for secondary grafts in animals in which the primary inoculation has led to tumors which ultimately are absorbed, and (3) for those seen during spontaneous healing. The part played by changes in the cancer-cell itself is brought out by the fact that, while one tumor is absorbed, another continues to grow in the same host.

SUMMARY

In a recent review of Ehrlich's standpoint, which is also his own, Apolant [1] covers very much the same ground that Bashford has, but there are a few divergencies, not so much as to facts, but rather as regards their interpretation. The most important differences as to facts are that Apolant has never observed any seemingly recurring fluctuations in the rate of growth and in the transplantability of tumors. While he agrees in believing it to be a general law that it is impossible to transplant tumors into a strange species, he claims, in opposition to Bashford, that it is possible to produce immunity by inoculating the normal tumors of strange species. The most important difference between the conclusions of these two schools, however, is as to the nature of immunity. While Bashford and his followers recognize only one form of active resistance, Ehrlich and his school hold that there is an additional form of immunity, viz., atreptic immunity.

In atreptic immunity the presence of a rapidly growing tumor so withdraws special food-stuffs that a second tumor is unable to establish itself if inoculated, and secondary growths cannot develop. Atreptic immunity is also found when a tumor grows only transitorily in a strange species, growth ceasing when the food-stuff transplanted with the cells has become exhausted. This interpretation of some of the experimental facts

[1] Apolant.—"Die experimentelle Erforschung der Geschwülst.," in Kolle u. Wassermann's Handbuch der pathogenen Mikroorganismen, Vol. III, 1913.

has been applied by Ehrlich to explain the etiology of tumors. Their origin is attributed to a decline in the appetite for food by the cells of the body as a whole, while isolated groups of cells retain a hunger more nearly the normal, or even, but only rarely, exceeding it. For a full discussion of these theoretical matters Apolant's valuable review should be consulted. Ehrlich's experimental results and deductions bring him into a certain amount of conflict with the facts of human pathology, which he explains away by stating that differences are due to human tumors not having such enormous proliferative energy as mouse tumors. It seems, however, that safer ground is occupied by those whose experimental tumors exactly reproduce the features of the disease as known in man, especially the power of dissemination.

Experiment has placed some old views on the nature and growth of cancer upon a new and firmer basis, by proving that, given suitable conditions, a small group of cells, when introduced into a healthy animal, will reproduce all the characteristics of cancer, namely, a primary growth, infiltration of the surrounding tissues, and secondary growths in internal organs and in the lymphatic glands. This experimental reproduction of the disease has been combined with the demonstration that the surgical removal of the inoculated cells prevents all evil consequences if the operation be performed sufficiently early; otherwise, recurrence takes place, or, dissemination having already occurred, death is inevitable. The surgical treatment of cancer is thus amply justified.

All the consequences of inoculating cancer cells can be prevented by a previous immunization, but, nevertheless, such immune animals can develop tumors of their own. Thus new and important evidence has been obtained that cancer arises not by the introduction of something from without (exogenous origin) but from causes peculiar to and within (endogenous) each individual organism.

The surmise that the growth of cancer is limitless, and independent of the rest of the body, has been shown by propagation to be a fact, embodying the real problem of cancer. The propagation of cancer has afforded opportunities for studying the biology of the tumor-cell, as regards its histology and the features of growth. It has been shown that histological structures may be lost; it has also been shown that the pictures often interpreted to mean that this was in progress in man, may signify the opposite, namely, a differentiation from young tumor cells. The tenacity with which typical structures may be retained and combined with powers of unlimited growth, has given experimental data which has been accepted by some as proving that the essential problem is the same for benign and malignant tumors, and that there is no sharp distinction between them, for example, according to the view of certain investigators, that there is a parasitic cause for malignant growths but not for those of non-malignant character.

Some facts, according to Bashford, stand out as having possible bearings upon the nature of cancer. Tumors vary in all degrees in their power to induce resistance to growth, and in their susceptibility to it, however induced. From mother material able to induce resistance there has been derived material which has lost this power, and which, while retaining susceptibility to resistance as a graft, has acquired powers of progressive growth for established tumors.

"A mere loss of power to induce hindrance to their own growth, on the part of a small group of cells in the circumscribed area within which a cancer arises, would not explain the origin of the disease. The influence of all the rest of the normal tissue, of the same and of different sorts, must remain dominant, otherwise the abnormal growth would be diffuse in the tissues in which cancer arises. The loss of power to induce hindrance to their own growth, combined with an insusceptibility to the hindrance elsewhere in the body, is an hypothesis having more to commend it. It is conceivable that a circumscribed group of cells may become insusceptible to the constitutional forces correlating growth, because of some modification analogous to that by which tumour-cells lose their power of inducing resistance, and that, although susceptible to it in strange hosts, they are indifferent to it in their hosts of origin.

"The delicate reactions thus far revealed are all of a new order, and are probably closely interrelated. They were not dreamed of a few years ago. At present their study appears to show that the etiology of cancer is complex, and compounded of both local and constitutional conditions."

SECTION VII

CLINICAL COURSE; DIAGNOSIS; POSSIBLE ERRORS IN DIAGNOSIS

CHAPTER I

CLINICAL COURSE

There is a certain amount of confusion in the way the terms benign (innocent) and malignant are applied to tumors. This is due to two circumstances. First, to the fact that these terms are used to describe the clinical course as well as the microscopical structure. Second, that, as there are all stages in structure, so also there are all degrees of malignancy. In neither case may a sharp line be drawn, although it has often been attempted.

In the section on Histopathology it has been made clear that for malignant new growths there are all gradations in structure, from complete retention of the normal character of a gland—the thyroid, for example—up to such entire loss of structure that it is impossible to refer the growth to its mother tissue. It is customary to infer the degree of malignancy from the extent to which the normal structure is retained. In a general way this can be done. An epithelioma, for example, showing very marked pearl formation—owing to great tendency to keratinization—would usually be held to be less malignant than one in which there was little such tendency. No hard and fast relation can be established, however, between structure and malignancy.

The bankruptcy of a purely histological classification is shown by the fact that occasionally pathologists in Germany have gone so far as to describe a "benign tumor with metastasis formation," meaning that, notwithstanding the retention of normal (benign) structure, the pathological findings and clinical course showed that clinically the tumor was really malignant.

Thus it comes about that the combination of the clinical course with the histological and pathological examination is the only reliable basis upon which the nature of a tumor can be determined with approximate certainty. Structure of itself is not a criterion of what the biological behavior of a tumor will be, although it is a useful guide. Clinical examination alone is often insufficient to determine either the nature of, or the treatment appropriate to, a tumor. Just as a careful clinician will call in the pathologist because he cannot make up his mind, so also the pathologist will sometimes not be able to come to a conclusion, and both together may be baffled or even proved wrong by the after course of events. In the present state of our knowledge, therefore, the essential similarity of tumors must be insisted on in connection with the progress and diagnosis of cancer.

The onset of cancer, as of any tumor, is insidious, and, in its earliest stages, without evident manifestations. The progress of the disease differs, not only as between one kind of benign or malignant new growth and another, and between one part of the body and another, but also as between the same kinds of growths occurring in the same sites, but in different individuals. Hence a general description must be a loose description. To avoid misunderstanding it may be explained that a malignant new growth, if allowed to progress, always causes death, whereas a person with a benign new growth dies with it, but not of it. Since benign and malignant new growths have but few properties in common, it can only be positively asserted of them in general that the vast majority, if not all, (1) arise in a single circumscribed area; (2) grow progressively up to death; and (3) if removed early enough are curable.

The earliest stage of cancer is an unrecognizable proliferation of cells which proceeds until it attracts attention in consequence of the appearance of a lump or an ulcer. An ulcer may supersede a lump, or, on the other hand, it may attract attention without any preceding lump having been detected. Plate IV shows the natural size and the microscopical structures of an early epithelioma of the tongue, and illustrates how small such an ulcer may be when its dangerous nature is already evident by signs of spreading into the adjacent tissues. An illustration is also given (Plate VII) of a nodule (natural size) in the breast, for which the entire organ was removed. Under higher magnification it is evident that at this early stage a small but rapidly growing soft carcinoma was present.

In these early stages, except for the presence of a lump in the breast or a small ulcer on the tongue, there are no symptoms.

Pain is entirely absent in the breast, and the slight inconvenience of an ulcer on the tongue would not suffice to send any—in fact none, except the most nervous and anxious—to the surgeon.

In this connection it should be emphasized that cancer is not necessarily painful at any stage of its progress, and particularly that pain is usually absent in early stages. The public are so obsessed with the painful and shocking nature of the disease that a "harmless," painless lump is too often neglected. Pain, however, may be present very early. When a nerve is involved it may be the first sign to attract attention; so also if bone is attacked, or if there is ulceration either on the surface of the body or in the alimentary canal. The later stages are usually associated with pain of all degrees of intensity. This applies more emphatically to all stages of the primary growth. After a primary or ulcerating tumor has been removed, metastases in internal organs may cause no pain and but little discomfort.

Whether carcinomatous or sarcomatous, the rate at which a malignant new growth increases in size varies greatly. Some grow very slowly, others very rapidly. A nodule in the breast may remain of about the same size for only a few months, or it may be several years; and an ulcer may even appear to heal. Some forms of round-celled sarcoma, and especially melanotic sarcoma, grow with alarming rapidity. But the rate of growth is not always a criterion as to the danger, nor of the rapidity of dissemination.

The size of the primary neoplasm may not indicate the real danger. For example, a minute melanotic sarcoma may already have widespread secondary nodules all over the body and huge masses in the liver. A lesion that looks like a small ulcer on the tongue may really be spreading out, fan-like, into the muscles and along under the mucous membrane, and there may be such involvement of the lymphatic glands that an operation for what looks like early cancer of the tongue, will be performed only as a palliative measure, or as an operation insuring a comfortable prolongation of life.

A slow-growing and apparently innocent tumor may, after years, suddenly develop into a rapidly fatal form of cancer. As a rule, the rate of growth is quickest in the young. In the old it may be so slow, as in the atrophic scirrhus of the breast in old women, that such tumors are often best left alone. Progress is usually most distressingly rapid in healthy, robust individuals.

In many forms of cancer there are periods of improvement.

A rodent ulcer may be healing at one edge and extending at another. Similarly, in cancer of the breast, a period of quiescence or of actual amelioration may set in either in the primary neoplasm or in the secondary deposits. This may be hardly apparent, and may be the result of sloughing or of the ulcerating out of an invaded gland. Real periods of stay of progress, or actual diminution in size, to be followed by recrudescence, are by no means infrequent. While these periods of quiescence stimulate to a search for methods of controlling growths, they also awaken false hopes, and obtain credit for allegations of the efficacy of remedies of which these interesting phenomena are entirely independent.

The clinical course or progress of cancer is the exact counterpart of the histological or microscopical findings. From the limited area in which the continuous growth has started, the cells spread throughout the body, producing baneful effects everywhere, until death ensues. It is thus as essential, in studying the clinical course of the disease, to separate the primary effects from the secondary consequences of the growth, as it is necessary to separate the pathological and microscopical findings into primary and secondary growths. It is only by so doing that a true conception may be obtained of the local and the constitutional effects of the disease, as distinguished from the parts played in causation by changes limited to the cells confined within the circumscribed area, and by constitutional conditions which may obtain in the body as a whole.

At the risk of repetition it may be recalled that histological and experimental study, as well as surgery, agree in disproving the ancient view that cancer is primarily a "constitutional" disease, in the sense in which the term was used by Sir James Paget, in a debate before the Pathological Society of London in 1874 (see p. 108). Even more emphatically these methods of investigation dismiss as absurd the idea that cancer is an "outcrop" from deep-seated "roots" pervading the system as a whole, but only sending up offshoots to the surface at one spot. It is necessary to emphasize these points because of the recent wide dissemination, in the lay press and by quasi-medical books, of these antiquated notions, and because of the revival in the minds of the public of the old despairing doctrine that cancer cannot be cut out once and for all, but that if cut out in one place crops out in another. The facts of pathology, the normal clinical course of the disease, and the facts of surgical experience are one and all distorted or actually falsified by presenting them in this way.

The process of spread is exactly the opposite. From the primary focus itself the offshoots reach outward throughout the body as a whole, just as they spread to a neighboring tissue and produce their primary and secondary effects. In their immediate environment, according to their situation, they destroy the skin or mucous membranes, producing extensive ulceration; they also destroy the eyes, the ears, even cartilage and bone. By invading the walls of blood vessels, especially veins, they cause repeated and exhausting hemorrhage. They may press upon the esophagus or trachea, and may cause starvation or respiratory difficulties. Large and important organs like the lungs, kidneys, liver, pancreas, thyroid, stomach, and intestines, may have their functions seriously interfered with. These effects are all caused by the cancer-cells growing into or pressing upon their immediate surroundings.

The secondary consequences arise from the secondary growths which develop in the neighboring lymphatic glands and in distant parts of the body from the offshoots of the primary focus, so that what was originally occurring around it alone, comes to pass in multiple centers and in many parts of the body. Wherever a secondary growth is situated it may produce exactly the same effects as a primary growth. The earlier and the more numerous the secondary manifestations, the more quickly does the patient succumb. The progress of the disease to a fatal issue may be painless, as when a secondary growth in the brain produces unconsciousness. Death may be sudden; but too often it is lingering and painful, complicated by the secondary as well as the primary effects leading to extensive ulceration or abscess formation, with resulting septic poisoning.

There is a widespread misconception of the cachexia or wasting sometimes associated with the progress both of benign and malignant tumors. The condition is not specific for malignant disease, and the seeking of advice or the making of a diagnosis should never be delayed for its appearance. In the vast majority of cases it is a late manifestation consequent upon the advance of the disease, and it is no longer regarded as an antecedent constitutional condition upon which cancer develops. Where there is ulceration with septic absorption, or interference with the food supply—for example, chronic indigestion or stricture—then the so-called cachectic state is more frequent and usually more marked. Widespread dissemination is also often accompanied by marked cachexia, as is the occurrence of repeated hemorrhage.

The duration of life of cancer subjects varies within wide limits, from a few months to many years, and may be endured with little more than discomfort. It is usually assumed that the average duration of life is from two to three years.

Cathcart[1] has well summarized the clinical distinction between innocent (benign) and malignant new growths, and the mode of progress and of death, as follows:

"Since the terms 'innocent' and 'malignant' are so intimately bound up with this discussion, it is necessary that we should try at the outset to grasp their meaning when applied to tumours. The contrast between a characteristic example of each class of tumour is well expressed by Mr. Bland-Sutton—now Sir John Bland-Sutton—when he says 'The baneful effects of innocent tumours depend entirely upon their environment, but malignant tumours destroy life whatever their situation.'

"If, now, we try to see how it is that malignant tumours destroy life whatever their situation, we shall find that they produce their evil effects differently in different cases. It may be:

"(a) By excessive local growth, whereby the tumour absorbs for its own use nutriment which would otherwise have supplied the normal tissue;

"(b) By degeneration and hemorrhage, whereby the blood is deteriorated and wasted;

"(c) By local dissemination, in which case the tumour sends offshoots into the surrounding tissue at a little distance from itself. These offshoots form new centers of growth, and thus act like an excessive overgrowth of the original focus in exhausting the patient;

"(d) By infiltration of the surrounding tissues, the tumour invading and destroying all the structures which it touches;

"(e) By lymph dissemination, whereby the blood is the agent by which the foci are distributed to different parts of the body.

"These various ways of causing death may not be all present in the same case. Those which have been placed first are associated with the less malignant forms of tumour, and those at the end of the list with the more malignant forms. The less malignant manifestations are more frequently present alone, while the others are more frequently combined. Thus local growth may destroy life without any form of dissemination, but if local infiltration occurs, dissemination by the blood- or lymph-stream is generally present also. .

"One well-known practical test of malignancy is 'return after removal.' This, of course, means return after the removal of all visible portions of the tumour. Such return is an outcome of what has just been described as local dissemination, infiltra-

[1] Cathcart, C. W.—"The Essential Similarity of Innocent and Malignant Tumours: A Study of Tumour Growth," Bristol, 1897.

tion, or dissemination by blood- or lymph-stream. It depends upon the power of the cells to break free from the original focus and to develop a fresh mass of tumour-growth when carried to a new part of the patient's body. 'Return after removal,' therefore is not an additional manifestation of malignancy;[1] only an unfortunate way of clinically proving that certain malignant features have undoubtedly been present in a particular case.

"In contrast with 'malignant' tumours, those which are 'innocent' may be said to have characters negative to those of the malignant forms. A typically innocent tumour does not injure its host's life by excessive growth, it does not infiltrate the tissues which surround it, and it does not give rise to new tumours either by 'local dissemination' or at a distance, when carried by the blood- or lymph-stream. While, however, it is possible to say all this of some tumours, there are others in which the line of demarcation between the innocent and malignant characters is not a sharp and well-defined one. In other words, the two classes of tumour are not distinct, but differ only in degree."

Death may come on suddenly and painlessly from hemorrhage or embolus, long before it would occur mercifully from sheer advancing enfeeblement. Often, however, it only follows upon a long period of suffering from a discharging, ulcerated surface. At certain sites, when communications become established between one viscus and another, there may be other and even more distressing complications. Many patients die *with* cancer but not *of* it, owing to the merciful intervention of some other illness. Many die in relative comfort, not of the primary growth, which has been cured, but of the secondary deposits in internal organs.

In concluding this sketch of the natural progress of cancer, reference must be made—since animal experiment has given to it additional interest, and has eliminated skepticism as to its occurrence—to the spontaneous cure of the disease. But owing to the faulty manner in which the pathological details of the cases of spontaneous cures[2] are described, it is impossible to estimate how frequent this occurrence may be. For cancer of the mamma in mice it has been determined that it does not occur once in a hundred cases; it is not more frequent in the human subject.

[1] It is often falsely so represented, as in the case of quacks who offer to cure cancer provided it has not been touched by the knife. *Vide* preceding page (183) with reference to "roots" of cancer.

[2] See General Bibliography.

SUMMARY

Careful study of the clinical course of cancer, as revealed in the hospital and the experimental laboratory, emphasizes the necessity of correlating clinical observation with histological and pathological examination, in order to determine the true nature of a tumor.

Accumulated evidence so obtained leads to the inevitable conclusion that cancer is absolutely local in its beginning, extension taking place from this primary focus.

The rationality of the early surgical removal of this localized manifestation, and the possibility, by this means, of effecting a cure, are given additional proof by the study of the clinical course of the disease.

CHAPTER II

DIAGNOSIS

CLINICAL

Cancer may be suspected, by patient or physician, in consequence of pain, a tumor, an ulcer, or prolonged indigestion; or the first cause of alarm may be jaundice, and, in the case of the uterus, hemorrhage. The complaint may be even more vague—"loss of flesh," "unhealthy appearance," or it may be quite indefinable on the patient's part.

The foregoing clinical description will have made clear how difficult it is at times to determine the exact nature of a patient's illness, even in the presence of an obvious tumor. A distinction may be drawn between external and internal growths, since in the case of the former, inspection and examination can be more complete. The difficulties are greater in internal conditions, especially if attention be not aroused by a visible or palpable tumor. The relative difficulty is well brought out in the table on the errors of diagnosis (Section VII, Chapter 3, p. 195). It will also be equally obvious that the history of the tumor, if one be present, is not an absolute guide.

On the surface of the body, or where the site is easily accessible, very careful inspection and palpation or the handling of the suspicious area are possible without accessory methods of diagnosis. In other sites, such as the stomach, intestines, rectum, esophagus, bladder, etc., special methods are essential, and such have been devised.

The clinical examination for the purposes of diagnosis takes special account of:

(a) Site (in limbs, bones, or muscles; in abdomen, wall, or what organ; secondary or primary).
(b) size (real or apparent).
(c) shape or contour, edge (cyst, lobulated or smooth).
(d) consistence, pulsation, translucency (cysts).
(e) movable or fixed (relation to surrounding tissue, skin for ulceration, bone, hollow or solid organs).
(f) vascularity, pulsation.
(g) auscultation (aneurysm, "wind").

In eliciting the necessary data upon which to base a clinical diagnosis of cancer, it has been my custom to use the following "Special Cancer History" blank. This also gives a convenient means of recording other data bearing upon the case, such as microscopic examination, previous treatment, subsequent history, etc.

SPECIAL CANCER HISTORY

Special Number............ Date....................
Name ....
Address ....
Case Number.................Service of...........................
Sex.............Age.............Married or Single...............
Nationality ....Occupation ....
If Female: Children................Miscarriages...............
Were Children Nursed?...
Any Breast Complications During Nursing?.........................
Any Lacerations of Cervix?................Perineum?..............
Condition of Teeth...
Prolonged Irritation or Traumatism Directly at Site of Primary Lesion
....
Prolonged Irritation in Close Proximity to but Not Directly at Site of Primary Lesion..
Place of Birth (Country, Town, or County).........................
Residence at Time of Onset of Disease.............................
Habits with Reference to:
(a) Alcohol ....
(b) Tobacco ....
(c) Drugs (Morphin, Cocain, Etc.).....................................
Previous General Diseases..
Previous Skin Diseases...
Previous Diseases Affecting Site of Cancer.........................
Diagnosis { Clinical...
Diagnosis { Microscopic..
Pathologist ....
Location of Primary Lesion...
Secondary Lesions..
Did Secondary Manifestations Follow any Form of Treatment?.........
....
Were There any Other Cases of any Form of Cancer in House or Neighborhood at Time Symptoms Were First Observed, or Within Recent Years?..
Note Particularly any Circumstances Suggestive of Contagion or Infection..
Family History with Reference to Cancer............................
Previous Treatment by Others.......................................
Treatment:
(a) Operative ....
(b) Medicinal (Enzymes, Sera, etc.)...................................
(c) Caustics ....
(d) X-rays ....
(e) Radium ....
(f) Fulguration ....
State whether (b), (c), (d), (e), (f) were used Previous to or Following Operation..
Eventual History...
Remarks ....

There is danger that palpation and other manipulative handling, if not done gently, may be the means of spreading the disease into surrounding tissues, lymph channels, and perhaps even into the lumen of veins whose walls are already infiltrated. (See Section XI, Chapter 1, p. 348.)

These considerations may leave a diagnosis uncertain. Exploratory operation is then resorted to, for the twofold purpose of ascertaining the true nature of the tumor, and of determining the appropriate treatment.

MICROSCOPIC

In all cases the clinical diagnosis should be accomplished by a microscopical examination of the growth by a competent pathologist, who should be fully in the confidence of the surgeon and have all the available clinical evidence placed at his disposal. Under certain circumstances it may even be advisable to have the pathologist present at the operation, especially if it be exploratory. While the patient is under light anesthesia a microscopic examination of sections may thus be made. Serial microscopic sections should be made in all except the most patent cases. A full history of each given case should be submitted to the pathologist, along with the section for microscopic study. The practice of simply submitting a preparation for microscopical study is to be deprecated, and it is gratifying to note that it is now largely abandoned. There is nothing more remarkable in the pronouncement of a skilled pathologist that the appearance under the microscope is that of a tumor, malignant or benign, where the subsequent course of events proves the opposite, than there is in the discovery, by the pathologist in the autopsy room, of the errors of the clinician, be he physician or surgeon. The interests of the pathologist and the surgeon are one and the same, namely, the best interests of the patient, even if doubts after a microscopical examination render it the wiser policy to treat as if a malignant new growth were present, although this is not known with certainty to be the case.

In perhaps the majority of instances the true nature of the growth can be discovered after the microscopical examination of a small number of sections of tissue removed for purposes of diagnosis. It is always to be borne in mind, however, that this may not be the case, and that the part which is malignant may not be found until many sections have been studied. It is also to be remembered that there is a possibility of a negative result being due to the presence of necrosis of tumor tissue, to the sloughing away of the base of an ulcer, or to cutting out a portion which does not reveal the true nature of the growth, for the simple reason that we have no absolutely certain criteria to guide us. A number of sections, cut in series, should therefore be examined in all doubtful cases. Small ulcers or growths may be sectioned from end to end and examined.

The following is a case in point:

Epithelioma of Lip and Glands of Neck.—J. L., male, aged 62. Thirty-five years ago the patient was bitten on the chin by a horse. The scar resulting from this wound is still visible, near the middle line, about on a level with the alveolar border. About five years ago the patient noticed a sore on the right side of the lower lip. This was indurated and tender. He was admitted to the hospital December 28, 1906. On December 30th, the mass, about the size of the end of the thumb, on the vermilion border, was removed, together with a V-shaped section of the lip. The glands of the neck, including the submaxillary, were removed. Recovery uneventful; no recurrence.

A pathologist of prominence reported the specimen to be absolutely non-malignant. Clinical evidence of malignancy being so apparent I requested further examination of the specimen. A number of additional sections were examined, with the final report of undoubted malignancy.

This case illustrates the fact that one should not lean too heavily upon a negative pathological report. The clinical evidence of malignancy in this case was conclusive, yet it was only after careful and prolonged search that microscopic evidence thereof could be found.

Many similar observations from my own experience and that of others, might be cited to emphasize this point.

SERODIAGNOSIS

The difficulties to which attention has been called have led to the active search for some means of diagnosing cancer by examining the fluids and excreta of the body, especially the serum and the urine. Every now and then a new diagnostic test of cancer is announced.

Diagnostic value is attached by some observers to the presence of some abnormal product in the urine, or to the excess or absence of a normal constituent.

Salomon and Saxl,[1] in 1911, suggested a test for carcinoma, based upon the supposed presence, in the urine of such patients,

[1] Salomon and Saxl.—"Eine Schwefelreaktion im Harne Krebskranker," *Wien. klin. Woch.*, 1911, xxiv, No. 13, 449; *Deutsch. med. Woch.*, 1912, xxxviii, 53.

of a sulphur-containing substance, which, treated with barium chlorid, yields barium sulphate. He reported positive results in 70 per cent. of cases. Others, notably Kaldeck,[1] Pribram,[2] Murachi,[3] and Petersen,[4] found the reaction positive in some cases of carcinoma. They attached little importance to it, however, for the reasons that it was not always positive in well-recognized cancer, and that it was positive in the presence of other diseases. Greenwald,[5] of Mount Sinai Hospital, New York City, tested the procedure, reaching the following conclusion:

"No differences were found to exist between the urines of patients with carcinoma and other diseases, and normal individuals, in the amount of barium sulphate, either absolute or relative to the total sulphur, precipitated by the procedure of Salomon and Saxl. It is therefore considered that the test is of no value in the diagnosis of carcinoma."

The methylene blue test in the urine of cancer patients, proposed in 1911, by Fuhs and Lintz,[6] was tested by Verbrycke[7] in 50 non-malignant cases, 4 cases of gastric carcinoma, and 1 probable cancer, with positive results in 15 cases, partially positive in 13, and negative in 27. Of the 4 cancer cases, it was positive in 1, partially positive in 2, and negative in 1. "From the number of positive results in certain non-malignant cases," he said, "it is evident that the test cannot even be credited with giving contributory evidence when positive. Again, if the test is of any value, it should certainly, in cases like the above, give positive results. Hence not even a negative reaction is of any worth."

Salkowski,[8] and Hess and Saxl[9] discovered that in the urine of cancer patients certain alcohol-precipitable nitrogenous substances are increased. Tests, too complicated to be of practical utility, were at first devised for the estimation of these substances, but later Salkowski[10] and Kojo proposed a simpler method, which, however, has not been found of dependable diagnostic significance.

Various serum reactions have been proposed. In the last few years alone there have been announced those of Brieger, Abder-

[1] Kaldeck.—*Wien. med. Woch.*, 1911, lxi, 1681.
[2] Pribram.—*Wien. klin. Woch.*, 1911, xxiv, No. 35, 1235.
[3] Murachi.—*Biochem. Ztschr.*, 1912, xli, 138.
[4] Petersen.—*Deutsch. med. Woch.*, 1912, xxxviii, No. 33, 1536.
[5] Greenwald, Isidor.—*Archives of Internal Med.*, 1913, No. 12, p. 283.
[6] Fuhs and Lintz.—*Jour. Am. Med. Assn.*, June 24, 1911, p. 1882.
[7] Verbrycke, J. Russell, Jr.—*Med. Rec.*, Oct. 28, 1911, p. 876.
[8] Salkowski.—*Berl. klin. Woch.*, 1910, xlvii, 1746.
[9] Hess and Saxl.—*Beiträge zur Carcinomforschung*, Heft. II.
[10] Salkowski.—*Berl. klin. Woch.*, 1910, xlvii, 2297.

halden, Freund and Kaminer, von Dungern, Ascoli modified by Kraus, and of other investigators of less prominence.

After a cancer has existed for a variable time, certain changes in the blood are noticeable, but just what these changes are, and the relation they bear to the disease under investigation, has not been clearly worked out. Indeed they do not appear to be present in every case of cancer, and a blood examination, even in an advanced case, may sometimes show a fairly normal picture.

In the majority of patients, particularly with cancers whose cells show a tendency to degenerative changes, anemia is found. But this is not distinctive of malignant disease, for it is found in many other conditions bearing no relation to cancerous growths, as well as in non-malignant tumors, especially in large uterine fibroids with their tendency to degeneration.

There appears to be, therefore, nothing specific of cancer in these changes, and they would appear to depend on various incidental causes and not on the presence of malignant cells.

In general it may be said that we find in cancer a progressive anemia—a gradual decrease in the total number of red blood cells, and a more or less marked, and often variable, leukocytosis. Concurrently with these changes we find a reduction in the hemoglobin—often to a very marked extent. Some investigators indeed have claimed that this reduction in the hemoglobin is found so early in the disease as to be of value in differential diagnosis.

In more recent years the blood serum of cancer patients has been made the subject of study in an attempt to demonstrate therein specific antibodies or ferments. Perhaps the better known of such reactions are those of Freund and Kaminer, of von Dungern and of Abderhalden.

Working on the principle that the blood serum of a normal individual has the power to dissolve cancer cells, while the serum of a patient suffering from cancer lacks this power, Freund and Kaminer have established a cytolytic reaction. Ten drops of the patient's serum, to which one drop of .5 per cent. sodium fluorid has been added, are mixed with one drop of an emulsion of cancer-cells. The mixture is placed in the incubator for 24 hours and then examined microscopically. Should the serum used be that of a cancer patient, no change is found, but if the serum has been taken from a healthy individual the number of cells is found to be materially reduced.

The method of von Dungern is comparable to the Wassermann reaction for syphilis. In applying it to cancer diagnosis the antigen used is made either from cancer-cells ground fine and extracted with 20 volumes of acetone, or from human blood, preferably that obtained from a patient suffering from general paralysis. Von Dungern prefers the latter method, in the use of which he has claimed over 90 per cent. positive reactions in cancer patients.

The serodialyzation test of Abderhalden has more recently been applied to cancer. Abderhalden believes that the blood serum of pregnant women contains specific ferments which have the power to digest placental cells. Other workers have endeavored to prove the existence of ferments in the serum of cancer patients which give them the power to digest cancer cells. The work is still in an experimental stage, and no definite conclusions can be drawn.

It is, of course, highly probable that the metabolism is disturbed in cancer, and that the fluids of the body may be different from the normal; such changes, however, if present, must be so subtle as to have escaped observation. Not one of the proposed tests can be relied upon. They are all non-specific and inconstant for cancer. Hence examination for the purposes of diagnosis is still almost entirely restricted to examination of the tumor or ulcer itself.

SUMMARY

The study of the clinical course of cancer and the difficulties involved in making a reliable diagnosis cannot fail to emphasize the importance of giving the patient the benefit of the doubt, on the positive as well as on the negative side.

One or more symptoms should not be relied upon in making a positive diagnosis of malignancy. Unless the clinical picture is absolutely convincing, especially in cases involving extensive surgery, microscopic study should be resorted to.

In the presence of a clear-cut clinical picture of malignancy, involving radical surgery, a negative microscopic examination should not be accepted. In many recorded instances, as in Case V, p. 200, malignancy has been discovered only after repeated sections have been examined.

No reliable serodiagnostic test for cancer has yet been proposed.

CHAPTER III

POSSIBLE ERRORS IN DIAGNOSIS

The frequency of over- and under-diagnosis has been emphasized by several writers. The fullest statistics have been compiled from the London hospitals by Bashford,[1] as given in the following figures and table:

"Out of 10,532 cases of cancer treated in hospitals, i. e., under the most favorable circumstances for diagnosis, 1,801 were not diagnosed as cancer from clinical evidence alone. Out of 9,488 cases treated as cancer, 757 were not suffering from the disease. The following table illustrates the relative proportions in which the disease was diagnosed in different sites of the body according to their accessibility to complete physical examination.

"The errors of diagnosis in general practice are probably not less than in hospitals, although, of course, no direct comparison is possible between hospital patients and the general population."

Analysis of the Cases of New Growths Reported by the Hospital Authorities (Microscopical Examination has been made in all Cases), 1904–09, all Ages

	Malignant New Growths		Wrongly diagnosed as cancer
	Correctly diagnosed	Not diagnosed	
Accessible	5,854	567	438
Inaccessible	1,555	945	159
Intermediate	1,322	289	160
Total	8,731	1,801	757
Accessible	91.1%	8.9%	....
Inaccessible	62.2%	37.8%	....
Intermediate	82.0%	18.0%	....
Accessible	93.0%	....	7.0%
Inaccessible	90.7%	....	9.3%
Intermediate	89.2%	....	10.8%

[1] Bashford, E. F.—"An Address on Cancer in Man and Animals," *The Lancet*, Lond., Sept. 4, 1909, II, p. 691.

The diagnosis and treatment, as cancer, of tumors which are ultimately found to have been of a different nature, has another interest. Of the cases operated on or examined at autopsy in the above table, as many as 757 were not cancer. There is no reason why the relative proportion of cases wrongly treated as cancer should be less in those refusing operation after clinical diagnosis. This explains very largely the extravagant claims made in certain quarters of curing cancer without the knife.

In the following pages I have endeavored to point out, by illustrative cases from my own experience, possible errors which may be made in the diagnosis of cancer of some of the regions most frequently involved.

HEAD

Case I. *Indurated mass in scalp, simulating malignancy, caused by foreign body.*—G. S., female, aged 50. Admitted to my service at the New York Polyclinic Medical School and Hospital, February 14, 1908. She gave the history of having first noticed, two years before, a small tumor on the top of the head. A few days after detection a scab formed over the center of the mass, and when this was removed there was a free discharge of purulent material, after which the slight soreness which had been present disappeared. The indurated area persisted, however, and from time to time a number of physicians in turn were consulted. The majority of those who examined it pronounced it "malignant," and advised the removal of the entire area under general anesthesia. The patient refused to consent.

Examination when I first saw her revealed a tumor of the scalp about the size of a silver dollar, a little to the left of the center of the occiput. Toward the center of this was a craterlike elevation in which was an opening. At the bottom of this opening could be seen a dark object. From the history of the case and from examination, the condition appeared to me to be more of an inflammatory character, caused by a foreign body of some kind, rather than malignant. I therefore advised removal of the tumor under local anesthesia. The entire mass was removed, the wound closed, and a dry dressing applied. Healing by primary union was prompt, and the patient has had no further trouble in this regard.

Examination of the mass revealed part of the tooth of a comb, which had become embedded in the tissues of the scalp, giving rise to chronic irritation, with subsequent inflammation and induration.

Careful microscopic examination showed no malignancy.

The points to be emphasized in this case are:

1. The clinician must ever be watchful for the unusual and unexpected.

2. Chronic irritation alone, even in those of the so-called cancerous age, does not always initiate a malignant process.

3. The importance of finer discrimination in diagnosis. Despite the stationary character of the growth, the absence of pain, and the presence of a palpable foreign body, a number of physicians had pronounced the condition malignant.

4. The promptness with which the tissues healed in the region where chronic irritation had existed for over two years.

Case II. *Epithelioma of the scalp, involving external table of skull and diploë.*—A. M., female, age given as sixty-five, in reality nearly seventy-five. Admitted to my service at the New York Skin and Cancer Hospital, January 16, 1908. Fifteen years before admission the patient had first noticed a small "lump" on the top of the head. This had grown slowly, but had given little trouble until a year before, when it began to grow very rapidly, to ulcerate, to bleed freely, and to cause considerable pain. She then went to the dispensary of one of the hospitals of the city, where for a year she was given antisyphilitic treatment. The conditions grew steadily worse despite this treatment, whereupon she was referred to me.

Examination revealed an ulcerating area of the scalp about four inches square. Upon operation this was found to involve not only the scalp, but the external table of the skull and the diploë. The entire area covered by the growth, together with a free margin of healthy tissue, was removed. The external table of the skull, with the corresponding diploë, over an area about two inches square, was chiseled away. The wound was packed. It was intended to perform a plastic operation after healthy granulations were formed, but this the patient obstinately refused to allow. She left the hospital at the end of three weeks, with the wound granulating around the edges.

On February 21, 1908, the patient was admitted to my service at the New York Polyclinic Medical School and Hospital, remaining under care for a number of weeks. Later she was treated in my dispensary service at the same institution. Gradually the entire area closed in and rounded out, so that new skin formed and the tissues underneath it seemed to correspond very largely to the structure of the normal scalp; even the bone of the external table of the skull appeared to be reproduced.

The pathological report was "epithelioma basocellare, of the papillomatous type."

Patient well when lost sight of four years afterward.

This case is interesting because of:

1. The extent of the malignant process and the involvement of the bone.

2. The complete recovery in a woman of advanced age.

3. The regeneration of the tissues, or their replacement by healthy tissue, without the intervention of plastic surgery.

4. The mistaking of an epithelioma, which had been practically stationary for fourteen years, and which had then suddenly taken on rapid growth, for syphilis, and the administration of anti-syphilitic treatment for a year, despite the continued development of the process.

Case III. *Intracranial tumor—epidural aberrant thyroid.*—M. S., female, aged sixty-two, married, native of Nova Scotia. First consulted me in October, 1906. Examination revealed a tumor, about the size of an orange, on the left of the head. This had gradually developed, according to the history, within three years, but had given no symptoms other than occasional severe headache. The eyes were slightly more prominent than normal, there was some pallor, suggestive of the early stage of cachexia, and the patient was very nervous. Otherwise she was in fair general condition. On the right side a goiter about the size of a hen's egg could be noted.

Examination of the tumor showed it to be not adherent to the skin, and to come from the external table of the skull or from within. A bony ridge could be felt around its base. The consistency of the tumor was masked by the tense pericranium and by the scalp overlying. No pulsation of the brain could be felt. I made the diagnosis of intracranial tumor, and advised an exploratory operation.

Previous to coming to New York the patient had consulted three physicians. Two of these made the diagnosis of sebaceous cyst, and offered to remove the tumor in their offices under local anesthesia. The third believed it to be a more serious condition, but being unwilling to operate himself he advised her to consult with some one who could cope with whatever it might prove to be. She then came to New York.

The patient was admitted to my service at the New York Polyclinic Medical School and Hospital, October 10, 1906. She was presented before the class in that institution, consisting of about fifty physicians, all of whom were given an opportunity to examine the case and make a diagnosis. Not one would agree that the tumor was intracranial, the consensus of opinion favoring the diagnosis of sebaceous cyst. Hematoma, lipoma, fibroma, dermoid cyst, carcinoma, and sarcoma were some of the diagnoses offered.

Believing it to be intracranial, I made an exploration and found that the probe passed down through the wound, straight into the skull. A small piece of the tumor was removed for examination, the strictest precautions of asepsis being taken, and the wound closed. The situation was explained to the family and the gravity of the condition made clear. It was decided to give the patient the chance offered by operation. Accordingly, I operated two weeks later. The tumor, which was the size of an orange externally, and almost as large internally, was removed. The dura was greatly thinned over the indented portion of the cerebrum. The hemorrhage was severe, but was controlled largely by pressure. The patient failed to rally, despite the use of the various methods of stimulation, including infusion, and died within two hours after the operation.

Dr. E. M. Jeffries, Pathologist to the New York Polyclinic Medical School and Hospital, gave the following report of postmortem examination: "Tumor of dura mater covering a portion of the left cerebrum. It was three and one-half inches in diameter, circular, and on the outer surface of the dura. Its upper edge bordered on the median line about three-quarters of an inch posterior to the middle. The growth was sharply defined upon the dura, but did not manifest itself on the inner surface. The brain tissue beneath was depressed for an area three and a half by four and a half inches. There was no evidence of absorption or inflammation of brain tissue.

"Microscopically the growth is somewhat doubtful in character. Judging from the clinical aspect it should be endothelioma; but sections of it would serve very well for demonstrating thyroid tissue. Structurally it is an adenoma suggesting aberrant thyroid."

Dr. James Ewing, Professor of Pathology, Cornell University Medical College, and Dr. William Elser, Pathologist to the New York Hospital, verified Dr. Jeffries' diagnosis with reference to the appearance of thyroid tissue, pronouncing it aberrant or "wandering" thyroid.

TONGUE

Case IV. *Gumma of tongue.*—J. T., male, aged thirty-one, admitted to the New York Skin and Cancer Hospital June 19,

1907. Negative luetic history given. Nine months before admission patient noticed a small "sore" at base of tongue, near the center of dorsum. During my absence from town the diagnosis of cancer of the tongue was made by six different doctors. When I returned the patient was on the table, ready to be anesthetized for operation for removal of the tongue. I made an examination and found a deep ulceration, about one inch wide, extending backward from the posterior two-thirds of the dorsum of the tongue to the epiglottis. The edges were irregular and elevated, and the floor uneven and coated. The edges were soft and friable. Cervical and supraclavicular glands were enlarged. I refused to operate, and immediately placed the patient upon antisyphilitic medication, with the result that the ulceration completely disappeared. The correctness of my diagnosis was further shown by the pathological reports from Dr. Martha Wollstein, of the Rockefeller Institute, and Dr. H. H. Janeway, Assistant Pathologist to the New York Skin and Cancer Hospital, both of whom rendered negative reports as far as cancer was concerned, each suggesting quiescent tuberculosis or syphilis as the probable condition. No tubercle bacilli were found.

Case V. *Epithelioma of tip of tongue,* early stage.—L. J. R., male, aged 41. The small nodule, together with a wedge-shaped section of apparently healthy tissue surrounding it, one inch long, removed from median line of tongue. Careful microscopic examination was made, not only of the nodule itself, but of sections taken along the healthy tissue. Microscopic examination of the nodule verified the clinical diagnosis. No cancer cells were found in the remainder of the wedge-shaped section of tissue until nearly the very apex of the wedge was reached. There a nest of suspicious cells was found, and a day later a longer angle was made by the removal of another small section at the apex of the wedge-shaped incision.

Had not a very thorough microscopic examination been made in this case, the removal of the nodule, with the wedge-shaped section of apparently healthy tissue, might have been considered sufficient. Recurrence would have been inevitable. As it was, the discovery of the nest of cancer cells at the apex of the wedge-shaped piece of tissue removed, and the wider dissection, have been followed by freedom from recurrence for over five years.

Case VI. *Carcinoma of tongue,* advanced stage.—E. S., male, aged 42. Absolutely negative history regarding lues. Patient had been an excessive smoker, always holding the cigar on the right side of the mouth. A number of years previous to consulting me he had first noticed a small sore on the dorsum of the tongue, half an inch from the right side and one and a half inches back. This would come and go, and was treated by diverse methods—nitrate of silver, antisyphilitic treatment (a positive diagnosis of syphilis having been made by the physician then in charge), X-ray, mixed treatment, etc. The growth was cut into by a dermatologist for the purpose of taking a section for microscopic study, and the report rendered that it was non-malignant. After going from one physician to another without benefit, the patient consulted Dr. L. Duncan Bulkley, by whom he was referred to me. The mouth was in a very fetid condition and the glands of the right side of the neck were involved. The disease was too far advanced for reasonable hope of cure, but not too advanced for operative procedure with the hope of relieving suffering and prolonging life.

The involved glands were removed and, at a subsequent operation, the tongue was completely excised. The patient gained in flesh and strength and was able to attend to his business for months. Recurrence finally took place in the neck, the patient was placed on the Enzyme Treatment (Case No. 76),[1] and died one year after I first saw him.

An early correct diagnosis and the institution of the proper treatment should have put an effectual stop to the malignant process in this case as it did in Case V. Cutting into the tumor doubtless materially lessened the patient's chances of cure.

BREAST.

Case VII. *Lipoma,* between pectoralis major and minor muscles, extending up under the clavicle, and pushing the pectoralis major and the breast forward.—Female, aged 34. The growth gave the appearance of tumor of the breast, and was so diagnosed by a number of physicians, who thought it was probably malignant. If it had been malignant, removal of the entire breast would have been necessary. It proved to be a multilobular lipoma, weighing three-quarters of a pound. Removed, without mutilation.

Case VIII. *Lipoma.*—This patient, female, 30 years of age, was presented, for diagnosis of tumor of breast, to the surgical matriculates of the New York Polyclinic Medical School and Hospital. The majority who examined her pronounced the condition probably malignant, and advised removal of the breast. This diagnosis and advice were not accepted. The tumor was removed by the author through an incision under the breast, and proved to be a small lipoma.

[1] Bainbridge.—See General Bibliography.

Case IX. *Lipoma; fibroademata.*—Woman, 32 years of age, gave a history of injury to left arm, and presented a tumor (*lipoma*) of left shoulder, and multiple tumors (*fibroadenomata*) of left breast, with retraction of both nipples. Pain in breast for several months. The history of pain, and the retraction of the nipples, might easily have led to the diagnosis of malignancy and to the removal of the breast. Such advice had been urged by some. Upon interrogation it was learned that the retraction of the nipples was congenital. The tumors were removed, and proved to be non-malignant.

Case X. *Fibrolipoma.*—Female, 54 years of age. Tumor in left axilla, extending to upper margin of left breast. Had been growing for five years, more rapidly of late, and had become painful. Nipple of left breast retracted. The cancerous age; a mass in the axilla, extending to the breast; retraction of the nipple on the same side; rapidity of growth of a previously slow-growing tumor; pain and discomfort in tumor—presented a picture strongly simulating malignancy. Yet the tumor, upon removal, proved to be fibrolipoma. The pain was doubtless partly psychic. In the presence of dense connective tissue, a fatty tumor in process of development may cause sufficient tension to give rise to pain and discomfort—leading, at times, to the clinical diagnosis of malignancy.

Case XI. *Necrosis of Rib, with Abscess.*—Female, aged 21 years. History of injury to neighborhood of sixth costal cartilage of left side, just under the breast, where she had pricked herself with a large knitting needle. An abscess formed, which was poulticed for a week. Abscess returned, with a resulting sinus which persisted to time of examination (about six months). Had had two operations, the sinus being opened and the bone scraped. Consulted me after two physicians had pronounced the condition malignant. Careful examination showed necrosis of the sixth rib and costal cartilage, with an abscess on the ribs. Incision below breast, breast lifted up, abscess evacuated, and diseased bone removed. The condition proved to be localized tuberculosis, with no evidence of malignancy.

Case XII. *Lumpy condition in both breasts,* with an indefinite mass in lower outer quadrant of right breast.—Female, 37 years of age. No distinct retraction of nipple, no enlargement of axillary glands. Diagnosis of malignancy had been made by two physicians, who advised against immediate operation because of patient's extremely neurasthenic condition. Growing steadily worse, she consulted another physician, who frankly told her she had cancer of both breasts. He treated her for some weeks with a cancer extract. She was also given galvanism for about six weeks. She then came to me. Examination revealed intestinal stasis, and this lumpy condition in the breasts. I told her she had no cancer, but she insisted upon being operated upon, and, to satisfy her, I removed two lumps from one breast. These proved to be benign. She was placed upon the usual non-surgical treatment for chronic intestinal stasis, and was told to wear breast supporters. The lumpy condition of the breasts cleared up completely, without operative interference.

CASE XIII. *Obstruction of Mammary Gland Ducts.*—Boy, between 12 and 13 years of age. Came into my clinic at the New York Polyclinic Medical School and Hospital almost crying, with a frightened look on his face, as if something terrible were impending. His mother had consulted me a few months before with cancer too far advanced for anything to be done surgically. She was treated with palliative measures for some time, and finally died. The boy had discovered a swelling below the nipple of each of his breasts, more marked in the left. He came to the clinic with the firm belief that he had cancer. Friends had told him they were sure he had his mother's trouble. Careful examination revealed simply obstruction of the gland ducts, as sometimes found in the young. The condition was relieved by application, for a few weeks, of belladonna ointment.

CASE XIV. *Sarcoma.*—Female, aged 55 years. Three years before noticed a small swelling, hard and nodular, in left axilla. Her physician told her to leave it alone. A month later an abscess developed, which was opened and treated for two weeks without improvement, and with the formation of fistulæ, which persisted despite treatment. After a succession of operations the mass in the breast continued to increase until it involved the left breast and almost the entire left chest wall. The condition was pronounced by several physicians *irremovable sarcoma* of the chest wall. By one she was treated for a time with a serum, without benefit. She was then given morphin and bromids and practically abandoned to her fate. Her suffering became so intense that Dr. I. A. Stoloff was called in by the family with the request that he euthanize her. He called me in consultation, and the patient was sent to the hospital. The tumor in the breast proved to be a tuberculous abscess, with no evidence of malignancy. I cleared out all the tuberculous tissue, which required an extensive operation. The patient made an uneventful recovery, and is well to-day.

ABDOMEN.

Not so many years have elapsed since the abdominal cavity was a veritable *terra incognita*. In many respects, and to some physicians and surgeons, it is still a world of mystery. It has furnished a convenient hiding place for many of the budgets of diagnostic error which have made so large a part of the history of medicine and surgery. And yet, within its hidden recesses have been performed some of the most brilliant and daring feats of surgery.

With the general progress in medicine and surgery which has marked the last quarter-century, modern methods of diagnosis, chemical, bacteriological, physical, and electrical, have brought us into intimate acquaintance with this region and with the diseases to which its contents are subject, enabling us, with a fair degree of accuracy, to predict what will be revealed by operation. In many cases, however, it is impossible, by any external diagnostic methods, to ascertain the exact conditions to be dealt with, and consequently we are unable to apply effectual remedial agencies. In such cases exploratory laparotomy comes into requisition.

The cases given below emphasize the importance of exploratory laparotomy, not as a last resort, but as an early means of making an absolutely correct diagnosis, not only as to the presence and extent, but as to the site, of cancer. The most telling arguments in favor of opening the abdomen and of seeing and feeling the actual state of affairs, are cases in which patients have been allowed to go untreated, or to be incorrectly treated, until it is too late for curative surgical intervention; and cases in which, through inexperience, perhaps, the surgeon is unable to make the correct diagnosis, even when the abdomen is opened. More frequent resort to exploratory laparotomy, and the development of skill in differential diagnosis when this is done, would be the means of saving many lives, and of prolonging the life-span of many more.

The following cases are selected to illustrate six of the more common sources of error in the diagnosis of abdominal cancer.

Type I.

Cases Diagnosed as Cancer, with no Cancer Present.—This is not an uncommon class of cases, for the reason that there are so many conditions which, without exploratory laparotomy, may be easily mistaken for cancer of some portion of the abdominal contents. The real condition may easily be amenable to surgical intervention and cure, yet the patient may be considered incurable and operation of too little avail to warrant the supposed contingent risks. The following is a list of some of the conditions, the symptoms of which may lead to the diagnosis of abdominal cancer:

1. Appendicitis with abscess formation (Case XV, Type 1).
2. Tuberculosis of kidney, liver, spleen, etc. (Case XVI, Type I).
3. "Stomach trouble"—healed ulcer, with pyloric stenosis (Case XVII, Type I).
4. Stone in kidney, with cachexia, etc. (Case XVIII, Type I).
5. Gall-stones.
6. Apparent tumors of stomach. (Kemp.) Conditions mistaken for:
   (a) Prolapse of left lobe of liver.
   (b) Pulsating aorta.
   (c) Thickening of abdominal muscles (recti).

Gastroptosis is usually associated with these conditions; consequently there is generally a long history of *emaciation.*

10. Simple adhesions of the stomach, generally following gall-bladder disease, gastric ulcer, or localized peritonitis.
11. Syphilis, according to Kemp, unless very careful examination is made, may present symptoms which simulate carcinoma of the stomach. He cites three cases. (Case XIX, Type I, illustrates this point.)

Kemp's cases:
   (a) Sclerosis of stomach.
   (b) Cirrhosis of liver.
   (c) Stenosis of pylorus, due to gummatous tumor, simulating malignancy.

12. Aneurysm of celiac axis simulating carcinoma of pylorus.
13. Chronic gastritis.
14. Nervous gastralgia.

The following cases illustrate this class of mistakes:

Case XV.—M. E. F., female, widow, aged 56, ten children.

Previous History.—Two years previous to consulting me, October 21, 1912, was operated upon for right inguinal hernia. A large sinus formed in the hernial wound. When first seen had been losing flesh and strength for a year. Considerable apparent cachexia. Large abdominal tumor, which had increased in size, occupying the center of the abdomen, seemingly connected with the stomach and intestine. This had been diagnosed by several as irremovable cancer, and she had been told that she was incurable. Sought relief by some form of serum treatment, for this purpose going to several dispensaries and hospitals, from which she was sent away with no hope.

Physical Examination.—Careful physical examination raised a grave doubt as to the presence of cancer. Exploratory laparotomy advised.

Operation, New York Skin and Cancer Hospital, November 16, 1912. A mass the size of a child's head was found in the lower portion of the abdomen. It was made up of great omentum enveloping a large abscess, in the center of which was the appendix. The appendix was removed, adhesions broken up, and abscess drained. There was no evidence of cancer. The sinus in the right side led down to an unabsorbed stitch, and was curetted.

Subsequent History.—Uneventful recovery. The cachexia, which was due to low-grade sepsis, not cancer, disappeared. January 1, 1914, perfectly well and strong.

Case XVI.—Mrs. G. A. A., aged 50. One child. Referred by Dr. Cora M. Ballard, of Brooklyn, February 15, 1909.

Previous History.—Pain of long duration in left side, with gradually growing tumor in same region. Loss of strength and flesh, with chills. Marked cachexia. Urine negative. Consulted a number of physicians and surgeons, some of whom made the diagnosis of irremovable cancer, involving kidney, spleen, and liver. Dr. Ballard was called and doubted the utter hopelessness of the condition, and, in a last effort for relief, with no thought of cure, I was called to see the patient.

Physical Examination.—Mass in left upper quadrant of abdomen, size of liver.

Diagnosis.—Abscess of left kidney.

Operation, New York Medical College and Hospital for Women, February 22, 1909. Ureteronephrectomy for pyelonephrolithiasis, with perinephric and priureteral abscesses. Evacuation of about a quart of pus.

Pathological Report, Dr. Louis René Kaufman.—"Acute pyonephritis. Abscess of pelvis and kidney, due probably to the *Bacillus coli communis,* with multiple calculi of urates and uric acid.

"Miliary abscesses are present in both medulla and cortex among remnants of kidney tissue, with advanced necrosis and hemorrhage; very little kidney substance is left and none is normal in sections examined."

Subsequent History.—Uneventful recovery. March 30, 1910, a sinus formed in the scar, which was curetted. It healed, but later formed again. In November, 1911, a new sinus started, whereupon the patient was given an autogenous colon bacillus vaccine. Perfectly well ever since.

CASE XVII.—W. H. B., male, aged 46. Referred by Dr. C. R. Woods, of Hamden, N. Y., February 12, 1909.

Previous History.—"Stomach trouble" for six years, growing steadily worse. For two years vomited "by spells." Coffee-ground material for the past year. Loss of flesh and strength.

X-ray Examination, by Dr. Lewis Gregory Cole.—"Hourglass contraction of stomach, with dilatation of the upper segment of the hook, just above the constriction on the lesser curvature. . . . Whether this is from an old scar or a new growth I do not feel justified in stating."

Diagnosis.—Chronic indurated ulcer, with probable malignant change. Impossible to determine the exact nature by other means than exploratory laparotomy. All other usual diagnostic methods employed.

Operation, New York Polyclinic Hospital, April 5, 1909. Large mass found at pyloric end of stomach, causing considerable pyloric stenosis. The diseased area was so large, and the glands so enlarged that if the condition were malignant the removal of the mass and of the diseased glands was hardly possible. However, believing it to be probably benign, it was decided to resort to posterior gastro-enterostomy.

Subsequent History.—Uneventful recovery. Marked gain in flesh and strength. Pains slowly disappeared. Perfectly well and strong, January 1, 1914.

CASE XVIII.—L. C., male, railway engineer, aged 69 years. First seen at one of the suburban hospitals, May 7, 1909.

Previous History.—Had had stone in the bladder twenty-five years before. For many months had been slowly losing flesh and strength, with pain in the abdomen, and the appearance of a slowly growing tumor, which was diagnosed as cancer of the stomach, involving the left kidney and other abdominal organs. Pronounced inoperable, and patient sent to hospital, January 8, 1909, for palliative treatment.

Physical Examination.—May 7, 1909. Markedly cachectic, very weak and emaciated. Made the diagnosis of stone in the kidney, with abscess, but no malignancy. Advised exploratory operation.

Operation, May 7, 1909. Diagnosis verified. Large stone found, with abscess formation within and around the left kidney, but absolutely no cancer. Stone removed and abscess drained.

Subsequent History.—On account of the patient's weakened condition, despite saline infusion and all other available measures, he failed to rally from the operation, dying during the same day.

The cachexia in this case, which was mistaken for that of cancer, was evidently of non-malignant origin. An exploratory laparotomy months earlier would have revealed the true cause of the patient's failing health, and would undoubtedly have saved his life.

Case XIX.—S. C. S., male, butcher, aged 33. Referred by Dr. W. B. Thompson, of Brooklyn, November 28, 1909.

Previous History.—History of "stomach trouble." Would vomit for days at a time. Pain very great after eating. Absolutely no specific history obtainable. Patient consulted several physicians, with varying results as to diagnosis. By some the trouble was pronounced ulcer of the stomach, by others locomotor ataxia, hyperchlorhydria, chronic appendicitis, and early malignancy. Received medical treatment, but without relief.

Physical Examination.—No evidence of a tumor, but a distinct area of epigastric resistance. Pain and tenderness upon palpation.

X-ray Examination, by Dr. Lewis Gregory Cole, showed constriction on the greater curvature of the stomach, very close to the pylorus. This constriction, although not very extensive, was persistent in all the plates, and was quite suggestive of carcinoma.

Operation, New York Polyclinic Hospital, January 14, 1910. Laparotomy. Appendix markedly diseased, containing two stones as large and longer than the phalanx of the index finger. Some adhesions around the appendix, and also around the outer side of the gall-bladder. No evidence of cancer of stomach, although wall congested and thickened.

Subsequent History.—Uneventful recovery from operation. Symptoms relieved for a time, but soon returned, becoming as severe as before surgical treatment. Symptoms continuing, a Wassermann test was made early in 1912, with positive findings. He was given "606," followed by inunctions of mercury, with relief of all symptoms. Well April 1, 1913.

In connection with this case it may be of interest to note that, in a series of cases examined by one of the Fellows of the Research Department of the New York Skin and Cancer

Hospital,[1] Wassermann test was positive in only two out of 212 cases of cancer. In one of these it was weak, in the other strong, and in both, specific disease was a possibility. In over 1,400 control cases of syphilis, the test, in each instance, was positive.

The case under consideration is an excellent illustration of the need, in obscure abdominal cases, of resort to all modern diagnostic measures, including those for syphilis. It is known that syphilis may cause various gastric disorders as well as constriction of the pylorus or other part of the stomach. The resulting symptoms may be easily confounded with those of carcinoma.

That this man had a badly diseased appendix and needed its removal was undoubtedly true, but appendectomy did not cure him of stomach trouble. Antisyphilitic treatment did.

Type II

Cases of Cancer, not Recognized as Such, but Diagnosed and Treated as Something Else.—Just as in the foregoing type the various conditions mentioned might be mistaken for cancer, so in this type, cancer may be mistaken for the various conditions named. Even upon exploratory operation the cancer may be overlooked, because of the presumptive existence of some other condition. Cases of this type call for the most careful observation of the entire field of exploration, in order that no focus of malignancy, however small, may be overlooked.

Case XX.—G. D., female, married, aged 45.

Previous History.—History of chronic intestinal stasis, with what seemed to be repeated attacks of appendicitis. Had been ill for many months with pain in right side; diagnosed as chronic appendicitis. Three weeks before admission was op-

[1] Fox, Frederick J.—"The Wassermann Reaction in Cancer," *Medical Record,* August 16, 1913, p. 283. See also:

Caan, A.—"Ueber Komplementablenkung bei Karzinom," *Münch. med. Wochenschr.,* April 4, 1911, LVIII, p. 731.

Newmark, L.—"The Occurrence of a Positive Wassermann Reaction in Two Cases of Non-Specific Tumors of the Central Nervous System," *Jour. Am. Med. Assn.,* Jan. 6, 1912, p. 11.

Foerster, A.—"Wassermann's Reaction in Relation to Cancer," *Lancet,* June 24, 1911, p. 1695.

Barrett, C.—"Ueber Komplementablenkung bei Menschencarcinom," *Zeitschr. f. Krebsforschung,* Berlin, 1911, XI, p. 245.

Pinkuss, A.—"Weitere Erfahrungen über Serologische Diagnostik Verlauf u. Behandlung des Karzinoms," *Deut. med. Woch.,* 1912, XXXVIII (2nd paper), p. 119.

Rosenberg, M.—"Zur Frage der Serologischen Karzinomdiagnostik," *Deut. med. Woch.,* 1912, XXXVIII, p. 1225.

erated upon and a mass confined to the head of the cecum and appendix was found. Cut into and drained.

Physical Examination.—Cancerous sinus at the site of the scar from the "appendicitis" operation. This was discharging mixed-infection pus. Mass in right iliac fossa.

Operation.—New York Skin and Cancer Hospital, December 12, 1912, exploratory laparotomy. The cancerous sinus was found surrounded by large and small intestine, which had become part of the sinus wall. The original growth was easily removable, and there were no glands which could not have been removed with ease. But the extension by contiguity to two feet of small intestine, cecum, and ascending colon made it impossible to thoroughly eradicate the disease.

Subsequent History.—Patient died a few days after operation.

This case emphasizes very strongly, not only the importance of careful diagnosis, previous to laparotomy operation, but also the importance of the *careful exploration* of the field involved. It is an excellent illustration of the danger of breaking down the barriers by means of which nature endeavors to protect the rest of the organism from invasion by cancer. When this patient was operated upon for presumptive appendicitis it is quite probable that the diseased tissue might have been entirely removed without danger of auto-infection of the other parts. Three weeks later extension had taken place so rapidly that complete eradication was impossible.

Case XXI.—D. Le R., female, married, aged 62 years. Admitted to the New York Skin and Cancer Hospital, April 3, 1912.

Previous History.—For a year and a half before admission had had the usual symptoms of chronic constipation, gastric disorder, vomiting, with typical symptoms of "biliousness," and a slowly growing mass in the right iliac fossa. Later, diarrhea. Diagnosis of gall-stones, with fecal retention in the ascending colon. Treated medically. Lost 12 pounds in weight. Diarrhea and cachexia had become quite marked by the time I first saw the patient.

Physical Examination.—Large mass in right iliac fossa, extending upward almost to the liver.

Operation, exploratory laparotomy, April 26, 1913. Cauliflower-like cancer of caput coli, extending up to the ascending colon, and acting as a valve, flapping against the ileocecal opening. Small intestine secondarily involved. Irremovable.

Exploratory laparotomy at an earlier stage, when the diagnosis of gall-stones was first made, would doubtless have rendered possible the thorough eradication of the disease. There was over a year of delay from the time of the appearance of the growth until the possibility of cancer was considered and surgical treatment instituted.

Case XXII.—A. H., female, widow, aged 48, three children. Admitted to the New York Skin and Cancer Hospital, November 27, 1908.

Previous History.—Seventeen months before admission patient began to suffer from "indigestion"—a constant burning behind the sternum, sometimes relieved by vomiting. Never vomited blood. Diagnosis of "nervous dyspepsia" made, and symptomatic treatment instituted. Vomiting increased in frequency. Great loss of flesh and strength. Upon admission to the hospital had been unable to retain any food for many weeks.

Physical Examination.—Mass in pyloric region size of an orange.

Operation, December 4, 1908. An irremovable mass, with enlarged glands way up behind the stomach and liver. Pylorus occluded. Retrocolic gastrojejunostomy performed.

Subsequent History.—Patient returned to the hospital June 11, 1909, complaining of vomiting after eating sweets—the first trouble after the operation. She was kept in bed for a time on restricted diet. Continued in good health until May, 1911, when, after exposure, she contracted a severe cough, acute tuberculosis developed, and the patient died in Bellevue Hospital, August 6, 1911.

This case emphasizes the importance of exploratory laparotomy in obscure abdominal conditions which, upon superficial examination, appear to be "indigestion," "nervous dyspepsia," etc. An earlier operation would doubtless have enabled the patient to live out her allotted span. As it was, by the palliative measure employed, she lived two and a half years in fair health and comfort, the immediate cause of death being an entirely different disease.

Type III

Cases of Small Cancer, diagnosed as Cancer, but having far more of something else present, the latter condition or conditions being mistaken for malignancy, or being considered too serious, in conjunction with the cancer, to warrant operative interference. Neglect in such cases allows an early and removable cancer to become advanced and perhaps irremovable; whereas, by exploration, it could be easily determined that the entire condition, including the small cancer, might be corrected by surgical procedure. Cases of this class are not so common as those of the first and second type, but undoubtedly many more would be found if exploratory laparotomy were more commonly and more carefully employed.

Case XXIII.[1]—J. L., female, married, aged 46 years. Admitted to the New York Skin and Cancer Hospital, April 29, 1907, referred by Dr. Henry McCastline, New York City.

Previous History.—Headache, pain in the back, dragging sensation on walking or standing, occasional vomiting. Enlargement of abdomen. Gradual loss of flesh and strength. Diagnosed as gall-stones, with an ovarian cyst probably undergoing cancerous degeneration.

Physical Examination.—Enormous enlargement of abdomen.

Operation, April 30, 1907. Laparotomy. Removal of right ovarian cyst, which weighed twenty-six and one-half pounds. Left ovary contained small cysts, and was the seat of a tumor the size of a hickory nut, which suggested benign carcinoma, and proved such upon microscopic examination. The left ovary and tube were excised. The appendix, which was bound down by adhesions, was removed. The gall-bladder was found much distended and containing gall-stones. The gall-bladder was stitched into a vertical wound just below the edge of the ninth costal cartilage. Two days later it was opened and fifty gall-stones removed. Free drainage was allowed. No cancer found elsewhere than in the left ovary.

Subsequent History.—Uneventful recovery. Perfectly well, April 1, 1913.

Believing that cancerous degeneration of the ovarian cyst, and perhaps of the gall-bladder and ducts, existed, operation was not undertaken by the surgeon first consulted. Exploratory laparotomy, however, revealed the fact that the very small cancer of the other ovary, and also the gall-stones, which were the real cause of most of the patient's discomfort, were amenable to surgical treatment. Without exploratory laparotomy these facts could not have been ascertained. Without the knowledge of the real condition, gained by such procedure, the patient would have been left to her fate.

[1] Reported (Bainbridge), with illustrations, in "Irremovable Cancer," *N. Y. Med. Jour.*, October 3, 1908, p. 625, being an abstract of the Fourth Annual Clinical Lecture on Cancer, delivered at the New York Skin and Cancer Hospital, April 22, 1908.

Type IV

Cases of Advanced Cancer, diagnosed as such, but made seemingly hopeless by an added condition which, in itself, is not of serious moment so far as prognosis is concerned. Correction of the complications in this type of cases is a matter of surgical technic, as is likewise the removal of the cancer.

Case XXIV.—G. H., married, female, aged 54. Referred by Dr. Henry Hughes, Long Branch, N. J., November 10, 1909.

Previous History.—Rectal trouble, with chronic constipation, for three years. In May, 1909, laparotomy was performed by another surgeon, with the purpose of removing a cancer of the lower bowel, but so many adhesions were found that nothing was done, the case being considered one of inoperable cancer, with general visceral extension.

Physical Examination.—Chronic intestinal stasis. Marked cachexia. Great loss of flesh and strength. Lower pelvic colon almost totally obstructed by advanced cancer of rectum.

Operation, November 22, 1909. With the hope that the first operator had been mistaken in the extent of the disease, and believing that if this were not the case a colostomy would give relief, exploratory laparotomy was performed. Extensive adhesions were found, but they were clearly from an old peritonitis following childbirth years before, and from the operation in May. These were separated. Diseased left ovary and tube found, salpingo-oöphorectomy performed. By the combined operation, using the vaginal outlet, 2½ feet of intestine, with mesorectum and mesosigmoid, removed. Cut end of rectum was brought into the pelvis. Sphincter, with last two inches of rectum, saved.

Subsequent History.—Uninterrupted recovery. Has at present some abdominal adhesions, necessitating the taking of cathartics, but has perfect control of bowel. Has gained 33 pounds in weight, and was perfectly well, Jan. 1, 1914.

This case emphasizes the importance of differentiating between malignant and non-malignant adhesions, between an inflammatory condition of tubes and ovaries (which pathological examination proved to be the case here, with no malignancy present) and cancer. Valuable time was lost by the failure to recognize these differences, and the patient was nearly sacrificed.

Type V

Cases in which the Error in Diagnosis Concerns the Stage of Extent of the Cancer. Seemingly inoperable and incurable cases may be operable and curable by resort to special methods, an example of which is the operation of arterial ligation, with "lymphatic block," described in Section XI, Chapter II.

CASE XXV.—C. U. S., female, widow, aged 44. Referred by Dr. Eliza M. Mosher, of Brooklyn, November 19, 1910.

Previous History.—Leucorrhea, sometimes tinged with blood, for several years, especially since laceration of cervix at birth of fourth child. Diagnosis of irremovable cancer of uterus made by two surgeons.

Physical Examination.—Evidence of advanced cancer of uterus, with apparent involvement of broad ligaments and pelvic glands.

Operation, Alston's Private Sanitarium, November 15, 1910. Arterial ligation of pelvic vessels, with "lymphatic block"; panhysterectomy, with vaginectomy (Wertheim).

Subsequent History.—Uneventful recovery, strong and perfectly well, January 1, 1914.

Had the opinion been followed in this case which was expressed before the Medical Society of the State of New York last year by one of its distinguished members, to the effect that when the glands are palpable it is too late for even a Wertheim operation, this patient would have been left to her fate. As it was, by tying off blood vessels and removing the glands along the ureters, from the obturator foramen to the receptaculum chyli, it became possible to do what seemed impossible before, and a complete removal of all disease was effected.

TYPE VI

Cases of Cancer in which the Error in Diagnosis Concerns the Type of Malignant Growth. One type, of a given stage of development, or of a given extent, may be incurable; another, of a corresponding stage or extent, may be curable. It is fair to assume that such cases are not of very common occurrence, but they are none the less important, and should always be borne in mind.

CASE XXVI.—R. V.,[1] female, married, aged 29 years. First consulted me May 19, 1907.

Previous History.—Patient had had an exploratory laparotomy in another city, the clinical diagnosis of round-celled sarcoma being made at that time, the growth being pronounced irremovable.

[1] Bainbridge.—(1) "Irremovable Cancer," *N. Y. Med. Jour.*, Oct. 3, 1908, p. 625.
(2) "Oxygen in Medicine and Surgery—A Contribution, with Report of Cases," *N. Y. State Jour. of Medicine,* June, 1908, p. 281.

Physical examination and the history of the case did not warrant, in my opinion, the diagnosis of irremovable sarcoma, and another exploratory laparotomy was advised.

Operation, June 12, 1907, at the New York Skin and Cancer Hospital. Papillomatous degeneration of the uterus, tubes, and ovaries found, extending to the intestines and well up on to the liver. A detached portion was removed for microscopical examination, the report being "malignant papilloma." Ten days later panhysterectomy was performed, and a large amount of fluid evacuated. A large papillomatous mass in the pelvis was also removed.

Subsequent History.—Since the above operations patient has undergone 10 laparotomies by the writer, making 12 in all, in addition to one by the other surgeon, and 67 tappings for the evacuation of serosanguineous fluid. About every six months the abdomen is opened, more of the papillomatous material removed, and oxygen usually introduced by the method described elsewhere.[1] The disease is much less extensive than it was nearly 7 years ago. The fluid still collects in the abdomen, necessitating tappings. The patient remains in the hospital two or three weeks after each laparotomy, and two or three hours after each paracentesis abdominalis. She has no cachexia, her bowels move regularly, her color is good, she weighs forty pounds more than she did 7 years ago, is able to do her housework, and, except for the discomfort experienced when the abdomen fills with fluid, feels perfectly well.

This case emphasizes the importance of differentiating the type of malignant neoplasms. Had this patient been the victim of sarcoma, or adenocarcinoma of a corresponding degree of extension when I first saw her, she would have been dead years ago. Had she been left without surgical intervention the malignant papilloma would have proved fatal long ago.

Moynihan, Rodman, Mayo, Kemp, Syms, Paterson, and many others have called attention to the necessity of early exploratory laparotomy. The statistics of many hospitals are illustrative of the frequency of mistaken diagnosis in abdominal conditions. The proportion of cases of abdominal cancer in which this disease is first recognized on the operating table or at autopsy, is variously estimated, according to the part involved, at from twenty to sixty per cent.

It is not to be inferred that exploratory laparotomy is advocated indiscriminately, or without a careful examination by all

[1] Bainbridge.—*Loc. cit.* (2).
See also: "The Intra-Abdominal Administration of Oxygen," *Annals of Surgery,* March, 1909, p. 305.

the diagnostic methods at our command, extending over a reasonable length of time. It is undeniable, however, that test-meals, gastroscopic examinations, X-ray exposures, and various other non-surgical diagnostic measures, with periods of trial treatment, may be the means, by virtue of the delay entailed, of plunging the patient into the slough of despond—the irremovable stage of cancer—when only palliative measures may be employed.

PELVIC ORGANS

Case XXVII.—*Cancer of the Breast and Uterine Fibroids.*—A. F., female, aged 48, private patient, referred to me for operation for *cancer of the uterus.* Right breast had been amputated four months previously by another surgeon. Shortly after recovery from this operation the patient had two uterine hemorrhages, and for the first time the physician made a vaginal examination. He found a large tumor in the uterus, and pronounced it a case of advanced cancer. He expressed to the husband his doubt as to the possibility of anything being done, but advised trying. I saw the patient in consultation and made a thorough examination. The uterus was retroverted, there was some fungous endometritis, and a fibroid the size of a large orange was found in the fundus. In the right side, where the drainage had been inserted at the time of the breast amputation, were a few small nodules, extending into the axilla. In the left breast was an actively growing malignant tumor, with lower axillary glands enlarged. The patient was sent away for a few days' rest in the country, and upon her return we removed the left breast, clearing the axilla, and curetted the uterus. Her condition has been much improved since the operation. A few nodules have appeared in the skin over the sternum, carcinoma *en cuirasse,* which seem to be diminishing under treatment with X-ray. Microscopic examinations of scrapings from uterus showed *simple endometritis.*

Case XXVIII. *Uterine Polypus.*—Single woman, 26 years of age, had had bleeding from uterus for some months. Profuse menstruation for some years. Diagnosis of uterine cancer had been made. Careful examination revealed no malignancy, but a polypus, which was snipped off, with resulting cessation of bleeding. Perfectly well since.

Case XXIX. *Cancer of the Uterus, Irremovable; Large Ulcerating Mass.*—W. S., female, married, aged about 50. Patient had always been apparently perfectly well until three years before operation, at which time she began to have some irregularity in menstruation and certain nervous symptoms, all considered as indications of the establishment of the menopause. There was gradual loss of weight and strength. Suddenly, and without special warning, an alarming hemorrhage occurred, in May, 1909. Dr. Ellis Hedges, the family physician, made an examination, finding a large, ulcerating mass in the pelvis. He tamponed the vagina, and demanded consultation. Eight distinguished gynecologists or surgeons were consulted. Curettage was proposed as the only possible operative procedure. This was attempted, under ether, by Dr. Hedges, but the extent of the disease and the friability of the tissues made thorough curettage impossible. Acetone was applied locally after this. The author was then called in consultation, and ligation of the arteries supplying the diseased parts was proposed by him. Accordingly, on May 8, 1909, at the home of the patient, laparotomy was performed. The cancer was found to be irremovable. The left ureter was obstructed by cicatricial contraction of the diseased tissue surrounding it. It was as large as the finger, and stood out like a whipcord. It was stripped up and freed from this constriction. Both ovarians, both internal iliacs, and the sacra media were ligated. Glands were removed to block lymphatic channels as much as possible. At the request of the family, radiogelatin was employed, two drachms being injected into the tissues in the neighborhood of the cancer in the body of the uterus. There was considerable collapse at the time of the operation, but the patient made an uneventful recovery.

The hemorrhage was absolutely controlled; the bladder symptoms which had been present before disappeared; the pain, weight, and tenderness in the obstructed left kidney were relieved by freeing the ureter; the discharge was lessened, and the general condition was improved. The patient gained sixteen pounds in weight, was able to preside at her own table, to take automobile rides, to go to the seashore, and later to the mountains.

At the time of operation she was given a general anesthetic, ostensibly for the purpose of making an examination and applying acetone, and so never knew that she had undergone a serious operation until long afterward, when she discovered the scar at the site of the abdominal wound. She never knew that she had cancer. She returned home in September, 1909, and after an illness of two weeks she died, probably from the shutting off of the kidneys by extension of the cancerous process. Death occurred October 2, 1909.

If the earlier symptoms had not been attributed merely to the menopause, and if the patient had allowed an examination, a correct diagnosis might have been made in the beginning and she might have been cured. Cases of this kind, which are all too numerous, should emphasize the importance of careful examination, and of periodical examination, in the presence of menstrual irregularities.

CASE XXX.[1] *Hodgkin's Disease.*—H., female, married, aged 43 years. Admitted to my service at the New York Skin and Cancer Hospital, March 17, 1911. Present illness began in November, 1910, with enlargement of glands of both axillæ. Two weeks later glands of right groin enlarged, then glands of neck, and finally there was general enlargement of the external glands to the size of a pea or greater. Upon examination the neck and breasts were found to be greatly swollen, and the skin tense over this area. Vaginal examination showed an enlarged uterus. The clinical diagnosis of sarcoma of the uterus, with metastasis in the lymph nodes, was made. The patient was under observation for three months. Inguinal nodes excised for examination showed necrosis. Axillary nodes excised a month later showed typical tubercle tissue with giant cells. Later examination revealed tubercle bacilli. Thickening and infection of the skin resulted from the patient's scratching. Sections of this thickened skin showed inflammatory changes, but nothing on which to base a diagnosis of new growth or of Hodgkin's disease. The patient died, June 25, 1911, apparently from exhaustion.

The uterus, upon post-mortem examination, was found to measure 12 cm. in length and 9 x 6 cm. at fundus. Surface nodular. Entire wall infiltrated with growth of dense fibrous tissue, which had caused apparent destruction of all the muscularis. Tubes presented similar nodular thickening at uterine end. Ovaries normal size; fibrous. Microscopical examination of sections of different parts of the uterus showed growth of endothelial cells, small round cells, with scattered giant cells. Portions were densely fibrous in character. The mucosa was almost entirely replaced by the growth, only a few scattered glands appearing in sections from the body and cervix. The nodules in the tubes and in one ovary showed similar changes. The appearance characteristic of Hodgkin's disease was found in the mesenteric, iliac, and bronchial lymph nodes, in the breast, and beneath the skin of the neck. The spleen gave evidence of recent involvement.

The diagnosis was made of Hodgkin's disease involving the

[1] Jessup, D. S. D.—"Hodgkin's Disease Involving the Uterus," *Am. Jour. of Obstet. and Dis. of Women and Children*, Vol. LXVI, No. 3, 1912, N. S. 12, p. 3.

uterus, tubes, and ovary. From the standpoint of clinical diagnosis the case is of interest, the enlargement of the uterus suggesting a new growth of an advanced, inoperable character, with metastases in most of the superficial lymph glands.

This was a rare condition. It served to emphasize the importance, in diagnosis, of considering as far as feasible all possibilities. The rare condition may be present in the case in hand.

SUMMARY

The fact that about 8 to 9 per cent. of the patients operated on for cancer or sent to the mortuary as dead of it were not sufferers from the disease has two very important consequences for the general public. The proportion is probably not less among the large number of patients who seek hospital advice, but who are either unwilling to undergo operation or are too late in seeking relief by this means. Many of these patients drift from one quack to another, or seek the aid of members of the medical profession who claim to cure cancer without the knife. This circumstance accounts very largely for the claims often made that a patient has been cured, after a diagnosis of cancer has been made by a distinguished surgeon, or a case has been pronounced inoperable by some hospital authority. On the other hand, the public should appreciate that not every lump or ulcer is cancerous, and that, owing to the difficulties of diagnosis, unnecessary fears ought to be allayed by seeking at once the advice of honorable members of the medical profession able to distinguish inflammatory swellings, especially syphilitic or tuberculous, from benign tumors, cysts, mere hypertrophic nodules, and malignant new growths. Morbid fears of cancer are often entertained by those who have had relatives die of it or have been brought in contact with friends so afflicted. It behooves all such not to nurse their anxieties, but to seek immediate advice lest the truth be learned too late for surgical aid, or dread of cancer needlessly darken the days of a perfectly healthy person.

SECTION VIII

PROPHYLAXIS

The prevention of cancer does not depend, as in the case of diseases known to be of specific origin, upon the destruction of the established causative organism or its resistant forms, or upon the removal of the definite and recognized source of contamination; it depends, rather, upon the elimination of one or more of a large number and variety of possible predisposing factors and precancerous conditions.

The predisposing elements which have been suggested and which are accepted by some as having greater or less etiological significance, are: race, sex, heredity, general nutrition, local nutrition, chronic irritation, repeated acute trauma, chronic inflammation, cicatricial tissue, benign tumors, and local manifestations of certain diseases, such as tuberculosis, syphilis, and diabetes, especially syphilis in the case of the tongue.

It has been said [1] that there is "scarcely an instance of a complete account of a case of visible cancer that does not give a clear precancerous history—a history of chronic irritation, ulcer, scar, hyperplasia, innocent tumor, or a combination of these factors." Experience and observation frequently bear out this statement.

Various other predisposing factors, such as climate, soil, occupation, and habits of life, are considered by some students of the cancer problem as bearing some relationship to cancer incidence. With the probable exception of alcohol, their significance, however, is not sufficiently well recognized to warrant any statements concerning the possibility of preventing the disease by the correction of these conditions.

Certain of the supposed predisposing influences, notably race, sex, and heredity, are beyond the control of the individual subject or of the physician and surgeon. Those which are subject to control or elimination may be grouped, for purposes of convenience, under the following heads:

[1] Crile, George W.—"The Cancer Problem," *Jour. Am. Med. Assn.*, June 6, 1908, p. 1883.

(1) Environment (diet, hygiene, occupation).
(2) Precancerous conditions (benign tumors).
(3) Local manifestations of other diseases, especially syphilis.
(4) Sources of chronic inflammation and irritation.

ENVIRONMENT

(Diet, Hygiene, Occupation, Etc.)

The influence of those factors which constitute the physical environment of an individual—diet, hygiene, habits of life, occupation, etc.—has been discussed briefly under the head of Geographical and Ethnological Distribution (Section II, Chapter 3); under Statistical Considerations (Section III); and under Predisposing Causes (Section IV, Chapter 2).

With the possible exception of occupation (workers in tar, soot, petroleum, and anilin), none of the elements of environment exert more than an indirect influence upon the incidence of cancer.

Any such effect may be said to resolve itself into the important factor—irritation. Thus a dietary régime which gives rise to persistent stomatitis, indigestion, and constipation may be followed by ulceration of the tongue or buccal mucous membranes, or by gastric or intestinal ulcer. Inflammation of the cervix uteri may arise from impacted feces in chronic constipation; and other chronic or oft-repeated irritations, for example, the frequent pricking of the finger in needlewomen, may furnish fruitful soil for the development of malignant disease. In the case of the intestinal canal the institution of a régime which favors proper assimilation and elimination helps to remove this element of danger, however remote it may appear to be.

With reference to intestinal cancer it is not to be inferred that the author subscribes to the views held by dietary faddists concerning the etiologic significance of given articles of diet. There is no proof of the influence of meat, of uncooked vegetables (as the supposed carriers of parasites which cause cancer), or of any other article of diet. The dietary régime is, in our opinion, of importance only in the maintenance of general health, and in the prevention of certain conditions associated with the predisposing elements in cancer production—chronic inflammation and irritation of the intestinal canal itself and adjacent organs.

The same may be said of general and personal hygienic regulations, as they pertain to ventilation, exercise, posture, wearing apparel, and the various matters which concern the maintenance of physical equilibrium.

PRECANCEROUS CONDITIONS

It is more than twenty years since Keen[1] first declared that pigmented moles may, under certain circumstances, develop into cancer. This contention has been abundantly confirmed by many surgeons since that time, and pigmented moles form only one of a long list of so-called benign conditions which come within the category of the precancerous stage of malignant neoplasms.

The term "precancerous" may be challenged because of the risk implied by waiting for cancer to develop, but the fact holds that, so far as we know to-day, certain local tissue manifestations which may continue a benign course in the life history of one individual may merge into a malignant course in another.

Among the so-called precancerous, or predisposing, conditions, the correction of which is a preventive measure so far as cancer is concerned, may be mentioned:

(1) Elevated angioma.
(2) Adenoma.
(3) Papilloma.
(4) Myoma.
(5) Adenoma.
(6) Xeroderma pigmentosum.[2]
(7) X-ray and other dermatites.
(8) Lymphangioma tuberosum multiplex.
(9) So-called benign cystic epithelioma.
(10) Rodent ulcer (really epithelioma of mild malignancy).
(11) Pigmented moles.
(12) Acanthosis nigricans.

If, as is now widely conceded, various benign conditions (by benign, meaning non-malignant or non-cancerous) may become cancerous, the responsibility for the prevention of some forms of cancer is in a large measure to be placed upon the general practitioner, the dermatologist, the gynecologist, or the specialist in whatever field, who is usually consulted for some purpose before the surgeon is called upon to operate for cancer.

It would be unwise to expect a practitioner of medicine in a

[1] Keen, W. W.—"The Danger of Allowing Warts and Moles to Remain Lest They Become Malignant," *Jour. Am. Med. Assn.*, 1904, XLIII, p. 96.

[2] Councilman, W. T., and Magrath, G. B.—"The Lesions of the Skin and the Tumor Formations in Xeroderma Pigmentosum," Fifth Report of the Cancer Commission of Harvard University, 1909, p. 5.

general or special field to give every patient a thorough physical examination for possible conditions which might lead to the initiation of malignancy. Patients would not submit to this, nor would the physician be willing, perhaps, to make the suggestion. Until, therefore, the campaign of education has sufficiently impressed the feasibility of such a suggestion, the most that can be expected is that in the course of examination and treatment for any given disease, the physician be watchful with reference to conditions which may be the precursors of cancer, advising the patient what to do in the circumstances peculiar to the individual.

In the light of actual experience, gained from the study of hundreds of cases, the author has formed the opinion that a large proportion of severe and often fatal malignant neoplasms may be traced to apparently insignificant and harmless warts, moles, nevi, and scars, which have been subjected to irritation of one kind or another, and which in earlier stages would have been easily and completely removable by surgical means.

Bloodgood,[1] from a series of statistical studies, reports that among 820 pathologically fully developed cancers of the skin and visible mucous membranes, he "was unable to find, in a well-taken history, the absence of a previous defect which might be looked on as a benign precancerous lesion." Among 997 epithelial tumors of the skin and visible mucous membranes, 173 were histologically benign. Of this group there was not in a single case a failure to cure.

In a group of cases of tumors arising in the derma, the subcutaneous tissues, the fascia, the sheaths of tendons and nerves, and the intermuscular connective tissue, Bloodgood [2] cites 406 distinctly benign cases and 132 sarcomas. In 48 of the sarcomas of the skin the malignant tumors developed in a nevus 8 times, in a scar 20 times, in a fibroma 9 times. In only 11 cases, therefore, could incrimination of the benign lesion be excluded.

The same author [3] reports 769 cases of malignant tumors of the breast, and 542 benign lesions. He calls attention to the fact that all the patients suffering from malignant lesions were 25 years of age, or older, at the onset of the disease; whereas, of the 542 patients with benign lesions, about 130 were under 25. "Therefore," he argues, "if a complete operation for cancer

[1] Bloodgood, Joseph Colt.—"Control of Cancer," *Jour. Am. Med. Assn.*, Vol. LXI, No. 26, December 27, 1913, p. 2283.

[2] Bloodgood, Joseph Colt.—"Diagnosis and Treatment of Border-line Pathological Lesions," *Surg. Gyn. and Obstet.*, Vol. XVIII, No. 1, January, 1914, p. 19.

[3] Bloodgood.—*Op. cit.*, p. 22.

had been performed for every lump in a woman over 25, about 50 per cent. would have been unnecessarily mutilated."

It is not to be inferred from what has been said that every tiny wart or mole, or other skin blemish, and every lump and bump on any part of the body, is to be ruthlessly removed. Many of the conditions which come under the category of pre-cancerous lesions, when not subjected to repeated acute traumatism or to chronic irritation, give no trouble in healthy persons whose lives are regulated on a well-ordered plane. In many instances, however, in a favorable host, and under favorable conditions, as when subjected to constant irritation or to repeated injury, these otherwise harmless lesions become definite sources of danger, and in such cases removal is obligatory.

LOCAL MANIFESTATIONS OF OTHER DISEASES

Certain pathological states, notably, tuberculosis (lupus), syphilis, leukoplakia (psoriasis linguæ), psoriasis (general), have been associated by different investigators with cancer as predisposing causes. Some hold that the same underlying diathesis which renders a person susceptible to tuberculosis or psoriasis, predisposes such an individual to malignant disease. The local manifestations of these diseases, as well as of syphilis, in which diathesis plays no part, are thought to predispose the subject to the development of cancer upon the site of the lesion.

The explanation of the causal relationship between cancer and these local manifestations of other diseases has not been definitely determined. By some it is thought to rest upon the basis of a certain tissue susceptibility; by others there is suggested the same or a closely related essential cause; and by still others the irritation theory is brought into play, as in the case of an old lupus scar or a long-standing tubercular sinus.

Whatever the explanation, the fact remains, as pointed out under Predisposing Causes (Section IV, Chapter 2), and as illustrated in some of the case reports appended, cancer is not infrequently superimposed upon local manifestations of other diseases, upon the tissue subjected to chronic irritating discharges, or upon the scar tissue which results from such local lesions, particularly when subjected to irritation.

Further consideration of the possible influence, as predisposing factors, of local manifestations of other diseases is reserved for the discussion of inflammation and irritation.

SOURCES OF CHRONIC INFLAMMATION AND IRRITATION

The fact, as stated in Section IV, Chapter 2, page 126, that a large part of the work of the Imperial Cancer Research Fund of London is directed toward discovering the explanation of the association between many forms of cancer with chronic irritation, gives an idea of the importance which is attached to this predisposing factor in the production of cancer.

The manifold character of irritants—which may be chemical, mechanical, actinic, or bacterial—is noted, and a large number of experiments and observations have been made in this connection.

It may be stated in general terms that, for purposes of prophylaxis, so far as cancer is concerned, no matter what the nature of the irritant, when its effects are sufficiently marked to become a menace, the cause of irritation should be obviated, whether it be a chemical irritant associated with occupation, an actinic irritation arising from X-ray or other burns, mechanical irritation, from the friction of wearing apparel, or bacterial, as giving rise to certain local predisposing lesions.

There are very few portions of the body which are exempt from one or another of the various kinds of irritation.

The upper part of the head furnishes an excellent illustration of the danger of chronic irritation (see case reports appended, Nos. I, II, III, IV, and V). As is well known, the upper part of the head, or above the mouth, is not so frequently the seat of malignant neoplasms as is the part which involves the mouth and the upper part of the neck. This difference is traceable, at least in a measure, to the relative paucity of blood supply of the scalp, forehead, and cheek. Yet in this region, as illustrated by the cases cited below, apparently very insignificant lesions, when subject to irritation, may eventuate in serious and fatal cancer.

The mouth is a common seat of malignancy, because of the wide possibility of irritation. The presumptive influence, in this connection, of leukoplakia and syphilis has already been indicated. Another very common source of irritation associated with cancer of the lip and tongue arises from smoking. The pipe, cigar, or cigarette, being always held in the same position, by mechanical irritation, by burning, or perhaps, as suggested by Lazarus-Barlow, by radioactivity, seems to initiate the cell proliferation which eventuates in cancer. It is important, therefore, for persons who cannot resist the inclination to smoke, to vary the position of the pipe, cigar, or cigarette, and thus diminish the possible danger of cancer.

Cancer of the tongue and buccal cavity is often noted in persons whose decayed and jagged teeth cause abrasions and chronic irritation of these parts. Malignant epulis and other malignant neoplasms of the alveolar process are often seen in persons with ill-fitting crown-and-bridge work or dental plates, or in those whose teeth are neglected and in bad condition. In such cases the dentist may play an important part in the prevention of cancer, and should coöperate with the medical profession in the campaign of education with regard to such matters.

The female breast is to be particularly well guarded with reference to the prevention of cancer by attention to the predisposing factors which involve this organ. Where the glandular tissue has been largely supplanted by the connective tissue of suppurative mastitis, a favorable condition for cancer formation apparently develops. Fissures of the nipple, the inflammatory affection of the areola and nipple known as Paget's disease, and areas subjected to chronic irritation by the corset, are particularly apt to become the seat of cancerous change. Attention to these, as well as to severe acute trauma of any part of the breast, will do much toward diminishing the risk of mammary cancer.

Other parts of the surface of the body are subject to malignant neoplasms apparently resulting from or associated with insignificant conditions. For example, a case of sarcoma of the foot is reported [1] as having developed following a blood-blister caused by wearing a tight boot. Five cases of melanotic sarcoma of the foot are reported in Kafirs [2] whose feet were full of deep cracks.

The association between cancer and chronic inflammation or irritation is fairly easy of demonstration upon the surface of the body. In the internal organs it is more difficult, for obvious reasons, and for some positions, for example, in the brain, the retina, and the new-born child, it is hardly conceivable that irritation, in the tangible sense here considered, plays any part whatsoever. It does not follow, however, that the tissues are incapable of irritating one another because of some disturbance of cell equilibrium, whether by internal secretion, or by other as yet unknown cause.

Cervical tears and metritis are commonly associated with cancer of the uterus. Chronic constipation, with fecal impac-

[1] *Brit. Med. Jour.*, February 11, 1882; also *Annals of Surgery*, March, 1898.

[2] Henson, W. Warner.—"Cancer in Kafirs: Suggested Cause," *Guy's Hospital Gazette*, March 26, 1904, N. S. 18, p. 131.

tion in the rectum, and the careless manipulation of the douche nozzle, are common causes of irritation in the presence of metritis and cervical tears.

In cancer of the stomach chronic gastritis, with its sequel, chronic gastric ulcer, mechanical lesions of the gastric mucosa, constant pressure in the gastric region, as is experienced by shoemakers, weavers, and similar workers, whose tools constantly press against the region over the stomach, and pressure by the corset in women who are given to the practice of tight lacing, are some of the predisposing factors mentioned in connection with gastric cancer. The importance of gastric and intestinal ulcer in the causation of gastro-intestinal cancer is a disputed question. Boas, Ewald, Hausen, Rosenheim, Lebert, and others, estimate the frequency of the transformation of simple ulcer into cancer, as five per cent. Mayo, Moynihan, Rodman, and others, have found a history of previous ulcer in as high as fifty per cent. of cases of cancer of the stomach. Paterson, on the other hand, does not recognize this relationship.

Cancer of the liver, gall-bladder, bile-ducts, and pancreas is thought to be initiated in a large proportion of cases in consequence of the irritation caused by calculi. Zenker (1889) found a history of calculi in 84.5 per cent. of all cases of hepatic carcinoma; Beadles (Cancer Hospital, London, 1905), in one hundred per cent.; Miodowski, in only $33\frac{1}{3}$ per cent.

The facts that bile-stones associated with cancer of the liver occur almost exclusively in women, and that the cause of bile-stone formation is generally referred largely to tight lacing, indicate that the abuse of the corset is indirectly connected with the development of cancer of the liver.

The importance of giving due attention to the predisposing factors discussed in the foregoing pages might be emphasized by a multiplicity of cases of cancer in different parts of the body. The following, however, selected because the lesions involved some portion of the skin and mucous membrane, and hence were visible and palpable, will suffice.

Cases are selected, in so far as is possible, which represent the apparently insignificant beginning as well as the direful eventuation of the condition. In many instances, for obvious reasons, it has been impossible to represent the beginning and the end in the same case. The series is made complete, however, by the presentation of similar conditions, at a given stage, in different individuals. In one or two cases both the early and the late stages of the disease appeared in the same individual coincidentally, but in different localities.

It is to be emphasized that some of the cases present conditions which, in themselves, are of no special interest, becoming important only in proportion to their liability to eventuate in something more serious.

In each case of cancer the clinical diagnosis was verified by microscopical examination. Unnecessary details are omitted for the sake of brevity, but the cases are so protocolled that future reference is possible.

For purposes of convenience the cases are grouped largely according to site-incidence rather than to the histologic characteristics of the lesions.

CASE REPORTS.

Case I.—G. R., male, aged 42, physician. In the left temporal region is a *small fibroma;* in the center of the forehead is a small *capillary angioma;* on the right side of the forehead is a small *pigmented spot.* The angioma is not elevated above the surface, and therefore is not of as much significance, as regards possible serious results, as is that in Case II.

Even flat angiomata, however, when subjected to constant irritation, may undergo malignant change.

The angioma in this case was removed by a confrère, without a scar, by means of mercurial caustic.

Case II.—H. C., male, aged 28, physician. In contradistinction to Case I, this patient has a small *elevated angioma* on the forehead. Subjected to chronic irritation or acute injury this is liable to undergo malignant change.

Case III.—H. S., male, aged 18 months. Shortly after birth a small *elevated angioma* appeared near the inner canthus of the left eye. It grew rapidly, projecting over and completely obstructing the eye. It was treated by the physician consulted by means of caustic applications. Following this there was ulceration, which did not heal, and the growth continued to increase in size.

The angiomatous mass was removed *in toto.* Serious hemorrhage was obviated by the use of silk threads, so placed as to partition off the angiomatous mass. Into each partition was injected a small quantity of carbolic acid. This caused complete coagulation, *en masse,* of the blood within the tumor, after which the threads were withdrawn. When contraction of the growth had taken place the entire mass was easily removed. Pathological examination showed distinct angiosarcoma.

The child, at the end of six years, is perfectly well, with practically no deformity.

Case IV.—M. O'C., female, aged 73. Epithelioma of left cheek, of twelve years' duration, originating upon *the site of a burn from a match.* A white scar resulted from the burn. Six years later, when repeatedly asked if the scar was due to smallpox, and when told that if she would make it bleed it would disappear, she began to pick at and scratch it until it bled. As the scab would form she would lift it off, not allowing the place to heal naturally. As a result of this an ulcer formed, which grew to such proportions that she sought medical treatment. From 1905 to 1909, with an interim of a month or so during these four years, she received X-ray treatment twice a week. The growth continued to extend. One year before admission to the hospital two other small growths appeared near the first.

The cancer, when we first saw it, was irremovable, and palliative operation in a woman of this age, with such extensive involvement, could hardly be expected to accomplish much. An ascitic fluid was employed for a time, after the method of Hodenpyl, but without effect. Radiogelatin was also used for a short time, but the patient objected to the reaction caused by these injections, and the treatment was discontinued before having been given a fair test in this case.

Thorough removal of the growth in the beginning would undoubtedly have resulted in eradication of the disease; or, better still, removal of the scar left by the burn, which was subjected to constant irritation, would have *prevented* the cancer.

The case illustrates the local nature of so many malignant growths above the mouth. We have here a terrific involvement, of many years' duration, with absolutely no metastasis in any other part.

The patient has lately returned to the hospital begging for relief during her last days.

Case V.—J. R. P., male, aged 72. Epithelioma of frontal region, with metastasis in parotid region, in cervical glands, and in lung. The upper nodule is a recurrence in the location of the primary growth. This first appeared as a *small nodule in the skin,* left side of forehead. It was cauterized by caustic applications, after which it healed. Soon afterward another nodule appeared lower down, nearer the inner canthus of the eye. Shortly after the appearance of this, recurrence took place in the scar of the caustic treatment of the first. Metastasis then appeared in the parotid region, which represents the patient's condition when he first consulted me. Examination revealed involvement of the cervical glands, and operation proved that there was an extension of the metastatic process to the lung.

Palliative treatment was all that was possible. Patient died from internal metastasis June 9, 1908.

We have in this case a history of early and terrific recurrence and metastasis (within seven months of the appearance of the primary growth upon the forehead) arising from a *tiny spot* in the region above the mouth, a growth which ordinarily would presumably be easily removable by the various dermatological measures often employed. Radical removal by surgical means might have been followed by recurrence, inasmuch as some cases of great malignancy seem to recur, no matter what is done, but certainly the chances of such a contingency would have been greatly lessened by a clean-cut excision of the primary growth when first noticed, with a safe margin of healthy tissue all around.

Case VI.—B. G., female, aged 46. Epithelioma of orbit and adjacent structures, involving eyeball and extending to the dura mater. The condition, which was of eight years' duration, began, according to the history, as a *small ulcer* on the lower lid, following a local diphtheritic infection during an attack of diphtheria. It developed slowly at first, and very fast for about one year before admission to the hospital. No treatment whatever was received, except with washes, salves, etc., during the eight years previous to admission.

In April, 1909, the entire growth was removed, including the contents of the orbit, together with its inner wall, down to the dura mater. The wound was packed with gauze and allowed to granulate preparatory to doing a plastic operation. A subsequent slight recurrence necessitated a second operation, when an area of the dura, about the size of a ten-cent piece, which was involved, was removed, exposing the brain. For a time the cerebrospinal fluid came from the wound. Finally, however, the area granulated over. Plastic operation was performed at later date.

There are no signs of recurrence at the present time, nearly five years after operation. In a letter the patient says she is "enjoying perfect health."

Case VII.—H. B., male, aged 74. Epithelioma of the tip of nose and left side of cheek, just below the eye, extending about one and a half inches from the nose. This began five years before admission as a *small wart-like excrescence,* easily removable. Six months later a growth under the eye developed from a similar beginning, and was also easily eradicable. The patient, in this case as in the preceding, neglected to seek medical advice until the conditions reached the proportions described.

Complete and thorough excision of the epithelioma was resorted to, followed by a plastic operation.

The patient promised to return upon the slightest evidence of a recurrence, and inasmuch as I have heard nothing from him for more than two years I take it that he has had no further trouble. He has moved out of the city. Address unknown.

Case VIII.—J. S. R., male, aged 69. Epithelioma of nose, face, orbit, and superior maxilla, which began in 1888 as a *tiny nodule* on the side of the nose. Instead of being eradicated completely by thorough excision, this was treated with caustics, curetting, and later with X-rays, despite all of which treatment it recurred again and again.

In February, 1910, an extensive operation was performed as a palliative measure. The entire contents of the orbit, the bony orbit, the nasal bones, and the upper part of the superior maxilla of the left side, were removed and the cavity was packed with a mild iodoform gauze, benzoin, shellac, and nosophen powder.

Pain was greatly relieved, the fetor and discharge were lessened, and the consequent discomfort to the patient and his family ameliorated. The patient was still alive in November, 1910, but was gradually growing weaker.

Case IX.—M. F. P., male, aged 50. Epithelioma of lower lip. This case is an interesting illustration of what thorough surgery will accomplish in a person evidently predisposed to the development of cancer. Twenty-seven years before I saw him a *small growth appeared on the lip,* a little to one side. This primary growth was thoroughly removed, together with the glands of the neck, by the late Dr. Andrew J. McCosh. For all these years the patient has remained perfectly free from cancer. The small growth for which he consulted me could not be called a recurrence. This was removed. Reasoning from analogy, the patient will be free from cancer, unless another new neoplasm makes its appearance.

Case X.—T. W., male, aged 48. Epithelioma of the face and neck, recurrent from *very small growth on the lower lip.* The primary growth was removed by the surgeon who was consulted in the early stage, three years before admission to the New York Skin and Cancer Hospital, but the cervical glands were not removed. This case is the antithesis of Case IX. In a very short time after the removal of the growth there was a tremendous involvement of the glands of the neck, with internal metastasis. When admitted to the hospital the patient was in such an advanced stage of the disease that no operative interference was warrantable. He died, about a week after admission, of metastasis, the original site of the growth being perfectly healthy.

This case emphasizes admirably the importance of removing the glands of the neck in every case of cancer of the lower part of the face and mouth, unless there are some definitely contraindicative circumstances, such as extreme age or a lowered state of vitality which would render such an operation absolutely hazardous.

Case XI.—R. R., female, aged 5 years. Sarcoma of face, extending from the lip as the primary seat. First seen at the New York City Children's Hospitals and Schools, Randall's Island, December 2, 1909. One year before admission to the hospital the patient noticed a *small swelling upon the upper lip,* said to look like a birth-mark. This continued to develop, and the growth was removed at Mt. Sinai Hospital. Following this the patient was treated at the New York Hospital for Ruptured and Crippled for eight months with the mixed toxins of *Streptococcus erysipelatosus* and *Bacillus prodigiosus* (Coley's Fluid), without benefit. The patient was subsequently removed to Randall's Island.

According to the history obtained from the mother, the family physician, who was consulted before the admission of the patient to any hospital, incised the growth on the lip, first from the outside, then from the inside, and irrigated at frequent intervals. The rapid development of the growth to a fatal issue within one year serves to emphasize the danger of cutting into a malignant growth. In view of the generally accepted belief in the auto-infectivity of cancer [1] it is reasonable to suppose that the growth was hastened in this case by the incision of the tumor.

The patient received only palliative treatment at Randall's Island, where she died shortly after admission.

Case XII.—V. M. W., male, aged 58. Epithelioma of ear, inside concha. Advanced, but removable. Condition began as a *small nodule,* first noticed about three months before he consulted me. This was excised, but early recurrence followed. X-ray treatment was then instituted and continued for five weeks, several times a week, but proved no check to the development of the growth. His physician then told him to go to the country for a vacation in order to build up his general health, so that the local condition would yield more readily to the X-ray treatment. The patient came to New York and consulted me.

[1] Bainbridge.—"Metastases Following Incision of a Sarcoma," *N. Y. Polyclinic Journal,* January, 1908, p. 17.

The entire auricle, middle ear, and part of the mastoid process were involved. All the diseased tissue, including the drum membrane, periosteum of the bones inclosing the external auditory canal, and part of the mastoid process was removed, the glands below the ear being extirpated first. Convalescence was somewhat prolonged by the existence of otitis media, but was eventually perfect, and the patient has remained well for more than four years, which have elapsed since the operation.

Case XIII.—B. H., male, aged 93. Epithelioma of right auricle, of ten years' duration. The ulcerating growth involved the entire auricle and contiguous post-auricular area. This extensive and very painful condition had its beginning in a *small pimple* at the masto-auricular junction. The patient constantly picked and irritated the growth until it underwent malignant change. For six years no medical aid was sought, then the physician consulted employed X-ray treatment for about one year without permanent benefit. Radium was systematically used by another physician for about two months, again without benefit, and with so much pain that it was abandoned. When first seen by me the involvement was so extensive that operation in so old a patient was considered futile. He was put on the Enzyme Treatment (Case 51), but after three months he insisted upon the discontinuance of the injections because of the pain which they caused. Died December, 1909.

Case XIV.—C. S., male, aged 56. Epithelioma of the left ear, extensive and advanced. Nine years before consultation the patient was *burned upon the ear with a hot cinder.* Before this had entirely healed he received a blow upon the ear, following which there developed the growth which eventuated in the condition described. A salve was used upon the ear by the first physician consulted. The treatment was employed for ten months, during which time the growth steadily progressed. The auricle was then partly removed, which doubtless involved the cutting into of the cancerous tissue. At any rate, this did not eradicate the trouble, and one year later the entire auricle was removed. Recurrence took place after an interim of a year, and the physician then consulted employed a caustic paste. Despite all this treatment the growth continued until, when first seen by me, the enormous involvement was found. Upon operation this proved to be very deep, involving the entire mastoid process, parotid gland, part of the parietal bone, facial nerve, and the overlying soft tissue. The structures involved were removed practically *in toto,* though it was not thought possible to remove all of the disease. The dura was exposed for an area two and a half inches in diameter. The extensive wound was packed and allowed to granulate.

At the present time, after more than two years, there is a small nodule of recurrence at the upper, and one at the lower part of the scar area, insignificant in size and causing no symptoms. (These have been removed.)

Case XV.—G. S., female, aged 18 months. *Nevus on shoulder; angiosarcoma* of forearm, early stage, about the size of a silver quarter. The nevus on the shoulder, which was elevated above the surrounding skin surface, represented the precancerous stage of the angiosarcoma of the forearm. The latter had exactly the same beginning as the former, but developed to the proportions found before its removal. The presumption is that the nevus on the shoulder would have run the same course had it been removed before malignant degeneration began. After an interim of three years there has been no return of either growth. Either one, neglected, would doubtless have had the same ultimate history as the similar growth in the next case.

Case XVI.—A. W., male, aged 55. Spindle-celled sarcoma of right shoulder, advanced stage. This developed from a *small elevated angioma,* situated in the same relative position as the nevus on the shoulder in the preceding case. As a schoolboy the patient noticed this little birth-mark, which was so situated that his suspender buckle rubbed over it, and constantly irritated it. This, in addition to a number of injuries, seemed to initiate malignant degeneration; at any rate, by the time he was fifteen years of age there was a tumor at the site the size of a hazelnut. Removal at that time, with a safe margin of healthy tissue, would in all probability have resulted in complete cure. This was not done, however, until later, when the growth had assumed much larger proportions. A conservative operation was then performed by the surgeon consulted, but in spite of this, recurrence soon followed, the neoplasm developed rapidly, and when the patient was first seen by me the deep structures in the neck, extending down between the main trunks of the brachial plexus, were involved. The enormous mass, with its deep extensions, was completely extirpated in January, 1908. The patient remained apparently well for several months after this operation, but finally died of internal metastasis September, 1909.

Case XVII.—A. F. L., male, aged 73. Carcinoma of hand; recurrence in axilla and chest wall. Twenty-three years before admission to the Skin and Cancer Hospital, in November, 1909, a *small papillomatous nodule* appeared on the dorsum of the left hand. For five years this received no treatment, then caustics were employed, and later X-rays were resorted to, without avail. When the patient entered the hospital practically the entire dorsum of the left hand was involved in the growth, and metastatic deposits were found in the chest wall and axilla. The forearm was amputated, the axillary space was cleared, and all diseased tissue of the chest wall removed.

At the present time the patient is suffering from internal metastasis, which, however unfortunate, is not as distressing for the patient or the family as is external cancer.

Case XVIII.—E. M., female, aged 25. *Papilloma of back.* From irritation by corsets the growth is beginning to undergo inflammatory change, which is a precancerous stage of cancer. With continued irritation, malignant degeneration is apt to follow.

Case XIX.—M. McG., female, aged 70. Epithelioma of left buttock; *papilloma of right shoulder.* This case represents the precancerous (shoulder) stage, and the cancerous (buttock) actively growing stage, in the same host. The epithelioma of the buttock began as an insignificant papilloma like the one on the shoulder, but being so situated that it was subjected to irritation it developed into a growth the size of a lemon. The small papilloma on the shoulder was not especially irritated and had not undergone degeneration. Both excised. Patient now well, four years after operation.

Case XX.—M. S., male, aged 22. Sarcoma of thigh and groin. From a starting point very much like a *small mole the size of a pea,* on the ankle, which remained so for years, then began to grow, recurrence took place on the inner aspect of thigh and groin. Seven months before admission, patient was treated with Coley's Fluid preceding and following removal of secondary tumor from Scarpa's triangle. When first seen by me internal metastasis had occurred.

Multiple sarcomata of leg and groin removed. Patient died August 27, 1910.

SUMMARY

Actual clinical experience, gained from the study of hundreds of cases similar to those presented above, has convinced us that a large proportion of severe and perhaps fatal malignant neoplasms may be traced to apparently insignificant and harmless warts, moles, and nevi, which are subjected to irritation of one kind or another, and which are easily and completely removable by surgical means.

Rational attention by physicians and laymen to these seemingly inconsequent conditions would undoubtedly tend to lessen the proportion of cases of irremovable and inoperable, and consequently fatal, cancer.

To keep a watchful overlook of all patients with reference to these conditions is the duty of every physician and surgeon, because it forms an important part of the *prevention of cancer.*

SECTION IX

THE INVESTIGATION OF "CANCER CURES"

DIVERSITY OF AGENTS EMPLOYED IN THE TREATMENT OF CANCER

The remedial agents which have been suggested or employed in the treatment of malignant neoplasms range in diversity from green frogs and witchcraft to "Christian Science" and modern Surgery.

It is not to be inferred that the dead past has buried its dead in this matter; on the contrary, the past has brought to the present many detachments of its army of therapeutic shades.

Owing to our continued ignorance of the etiology of cancer, we find in the midst of the scientific practice of the twentieth century, remnants of the ignorance and superstition of the earliest times.

It is for this reason, as well as for its possible historical interest, that it has seemed worth while to devote some consideration to this phase of the cancer problem.

Furthermore, the treatment of cancer conforms more or less to the law of the rhythm of motion. Remedies for the disease have had their days of popularity, their lapses into oblivion, and their revivals. In some instances this cycle has been repeated over and over again. This applies to many of the agencies which have been employed by the medical profession, as well as to those whose use has been confined to the "cancer quacks."

The employment of such diverse measures and methods, some of which are absurd and many of them harmful, is the natural outcome of the mystery which enshrouds the nature and cause of cancer. It has also been fostered by the difficulty which has always been experienced in differentiating the various forms of this disease from the *dermatological manifestations* of certain other maladies, and by the mistakes in diagnosis which have arisen from these factors.

If the various so-called cancer cures were employed only in hopeless cases, being used merely as adjuvants or as last resorts in the desperate effort to alleviate suffering, and if they were in no way harmful, nothing would need to be said concerning them. Unfortunately, however, they are often brought into requisition where more rapid and better established methods should be utilized. They form, therefore, the settings, in many cases, of the deplorable pictures of *tampering,* which are so often presented to the surgeon, the cancer hospital, and the "home for incurables."

The record is a very long one of remedies that have been employed empirically, discarded, and at a later time revived again and again in the treatment of cancer. So, too, with agencies which have seemed to possess some scientific reason for their advocacy.

When new "cures" are being exploited, or when old methods are being revived, it is but natural that the conservative element of the medical profession should remain skeptical. It is equally to be expected that more or less unscrupulous individuals within the pale of medical ethics should attempt to turn to their own advantage the conscientious efforts of those who are endeavoring to discover some non-surgical method of curing cancer. The surgeon, therefore, who, more than anyone else perhaps, has the duty imposed upon him of dealing with this state of affairs, is unwilling to subject his operable patients to experimentation with non-surgical methods which have never been "tried out" by those who are competent to judge of the merits of such methods. This attitude on the part of the members of the medical profession upon whom so great a responsibility rests has fostered the idea with many laymen that the surgeon is unwilling to test non-surgical methods for the cure of cancer.

As Secretary of the Department of Research of the New York Skin and Cancer Hospital, it has been my duty to receive and investigate many proposed "cures" for cancer, and to catalogue many which are in no way worthy of consideration. From this experience I have come to realize that there are certain aspects of this question which are not generally understood, either within or without the medical profession.

In the light of our present knowledge concerning cancer, no surgeon should hesitate to urge the patient to employ the only means at our command which offers a definite hope of cure from this scourge—surgical removal. So long as patients are willing to be operated upon, so long must surgeons operate, until some better method has been positively established. It has been established by experiment that all the consequences can be avoided by *cutting out* the pin-head of cancer inoculated into animals, and as yet *only* by cutting it out.

In the meantime, however, those who have at their command a great many cancer patients will have a sufficient number who are unwilling to undergo operation, or who, because of some complicating condition, are inoperable while the cancer is yet curable if surgical intervention were feasible, upon whom new measures may be tested with that degree of thoroughness which constitutes a fair test. It may be easily seen that to make such tests a surgeon must have a large number of patients, or have charge of a hospital with special provision for such cases.

It cannot be gainsaid that surgeons who are daily brought into contact with a large number of cancer patients, and hospitals which have ample provision for such, are not only willing but anxious to apply the scientific test to seemingly rational new methods of treatment.

The surgeon, however, must protect his patients from charlatanry, which is nowhere so rampant as in the treatment of cancer. He must make certain demands of the one who proposes a new method and who insists upon its being tried. He must have at his command the time, the facilities, and the funds for such a test, which is but simple justice to both his patients and himself.

It may be said, in passing, that in the majority of instances the surgeon receives no assistance from the originator of the proposed remedy. The test is demanded, with no seeming realization of what it implies, and, if it is not made, the charge of professional bias is urged.

WHAT THE SURGEON HAS A RIGHT TO KNOW OF A PROPOSED METHOD OF TREATMENT

Before subjecting his patients, in private practice or in hospital service, to experimentation with a new agent, the surgeon should be assured of certain points concerning the proposed remedy.

First, he should have evidence of the sincerity of purpose of the individual who proposes the new method—that his object is the furtherance of scientific research and the amelioration of suffering, and not merely the replenishing of his own coffers.

Second, he must know that the method has some legitimate claims to a basis of scientific principle—that it is not merely "inherited from generations of cancer curers," or "handed down to the family from the Indians," as is sometimes claimed.

Third, he must have ample assurance that the method offers a reasonable hope of doing more good than other known means, with clear proof that it will do no harm.

Furthermore, before taking up the investigation of a cancer "cure," it is the surgeon's right to demand:

(1) That the composition and method of preparation of the proposed remedy be given. In other words, no one should be expected to test a secret remedy. It is but fair to the patient, to the possessor of the remedy, and to the one who tests it, that the alleged efficacious ingredient or ingredients be disclosed. Objection is generally made to this requirement on the part of the possessor of the "cure," but the one who tests it should not yield the point. In the event of the "remedy" being offered for a price there is no guarantee that it is to become public property if not *disclosed.*

(2) That a reasonable scientific theory be furnished as justification for the desired test, or that authentic clinical evidence of the efficiency of the method in treating proved cases of cancer be produced.

Many of the more hopeful of the remedies which have been proposed from time to time have not been adequately tested before the demand has been made upon the surgeon or hospital that a case trial be given. In some instances, therefore (notably the Enzyme Treatment proposed by Beard), the requirement with reference to clinical evidence is waived as being offset by the scientific premises upon which the method is based. In very few instances, in fact, can this point be adhered to, for the reason, previously suggested, that only those who come in contact with large numbers of cancer patients can make adequate tests, and for the further reason that the originator of the new method, in many instances, is not in position to make any sort of demonstration of his theory. This is one of the chief difficulties encountered in this phase of cancer research.

At the New York Skin and Cancer Hospital there is a standing offer of a monetary remuneration to anyone who presents for trial a non-surgical method for the cure of cancer which will stand the test of application to the cancer sufferer. Naturally, the hospital reserves the right to judge of the merits of the claims to recognition; to make the test when it is deemed wise to do so; and to render the final decision as to the value of the method. In addition to revealing the exact formula, the sole condition upon which such a test is made is that the proposed method offers a reasonable hope of doing more good than anything known, and a certainty that it will do no harm.

There are on file something like sixty "cures" which, in one way or another, we have been importuned to try in the wards. Some of these, as will be seen later, have been tried; some are now being tried; others, after due consideration, have been refused test, while still others have been so plainly of the "quack" type that nothing more has been done than catalogue them as matters of curiosity.

From the list of proposed "cures," which includes all manner of things, from "live lobster and leek" to the elaborately evolved product of the biological chemist, we have selected from time to time such agents as seemed to meet the requirements above stated. Brief details of some of these tests are given.

WHAT CONSTITUTES A "FAIR TEST"

It is generally conceded that sporadic or isolated instances of cure of any disease by a given means do not necessarily serve to indicate the successful application of the method to the general run of cases. This applies quite as forcefully to cancer as to any other disease. It is also quite well understood that there is a curved line of betterment in the majority of cases, in spite of, rather than in consequence of any treatment. Any agent or method which chances to be employed at the time of the ascending curve of betterment is apt to receive credit for such improvement.

For these reasons we have become accustomed to the idea that proof rests only in accumulated experience. We are prone, therefore, to look with a certain degree of skepticism upon the claims to success which are founded upon a small number of clinical records. Yet who shall say just what that number must be? By what standards shall the fairness of a test be measured?

The late Dr. Maurice H. Richardson [1] held that "one single total disappearance of undoubted breast cancer under any form of non-operative treatment will presage success, just as surely as a successful man-flight presaged aviation." But what of the outlook for such a method if, succeeding in *one* case, it fails in *one hundred* cases?

[1] Richardson, Maurice H.—"The Operative Treatment of Cancer of the Breast," *Jour. Am. Med. Assn.*, February 4, 1911, p. 315.

THE ENZYME TREATMENT

(Trypsin and Amylopsin, Plus Régime)

Dr. John Beard,[1] one of the originators[2] of the enzyme treatment of cancer, accepts one case of recurrent sarcoma, in which the "remains of the tumor finally shelled out 'like the kernel of a nut'" under the enzyme treatment, as an undoubted proof of the correctness of the theory upon which the method is based, and consequently as proof of its curative value. At the same time he rejects, as practically no test at all, the painstaking trial, extending over three years, and applied in one hundred cases at the New York Skin and Cancer Hospital.[3]

The question then naturally arises: "What constitutes a 'fair trial' of a given method?"

The test given the enzyme treatment at the New York Skin and Cancer Hospital, according to our ideas, is an example of a "fair test," by which is meant a test that is conducted along scientific lines, justice to the patient, and justice to the theory upon which the method of treatment is based, being at all times borne in mind.

The charges have been made of the various tests of this method that they were not made with a sufficient number of cases to be conclusive, that the time during which the patients were under treatment and observation was too short, and that the test was begun with a preconceived notion that the findings would be negative. In this connection it is interesting to read the opinions of others with reference to our test of this method.

The *British Medical Journal,*[4] for example, referred to our report as follows: "It is a very extensive and elaborate document, with carefully tabulated details and charts." Czerny, before the Second International Conference for the Study of Cancer, held in Paris in 1910, referred to our test of the enzyme treatment as an example of thoroughness and of progress by negation. Rowntree[5] said: "Any doubts that may have lingered in the minds of those who thought the various

[1] Beard, John.—"The Enzyme Treatment of Cancer," 1911.

[2] "Discussion on Non-Operative Treatment of Cancer," Proc. Roy. Soc. Med., Therap. Sect., 1913.

[3] Bainbridge, William Seaman.—"The Enzyme Treatment for Cancer, Scientific Report on the Investigations with Reference to the Treatment of Cancer, Published with the Authority of the Committee on Scientific Research of the New York Skin and Cancer Hospital, 1909. See also: *New York Medical Journal*, March 2, 1907; *Brit. Med. Jour.*, March 2, 1907, pp. 486 and 519; *Medical Record,* July 17, 1909.

[4] *Brit. Med. Jour.*, July 24, 1909, p. 218 (editorial).

[5] Rowntree, Cecil.—Article on Tumors, in "A System of Treatment," edited by Arthur Latham and T. Crisp English, 1912.

details of the treatment had not been sufficiently extended, must surely have been finally dispelled by the report published by Dr. William Seaman Bainbridge, of New York." "This report," he continues, "deals with the results obtained in a large number of cases of cancer in which the trypsin treatment had received a most thorough and painstaking trial."

The test under discussion was made under the personal direction of the author, with the assistance of members of the Research Staff and others. It included more than a hundred cases; [1] it extended over more than three years; every detail was carefully observed; careful records were kept, and, throughout, the wishes of Dr. Beard, as expressed in numerous personal communications which we have on file, were observed. We entered upon the test with absolutely open minds, and maintained throughout the scientific attitude of suspended judgment pending proof.

Such a test may not conform to the ideas of fairness which exist in the mind of an investigator whose work has been along the lines of Beard. It would seem, however, that nothing more can justly be expected of the clinician, who, whether working in the laboratory, in the operating room, or at the bedside, must at the same time be true to his human obligation to the patient.

It is to be regretted that, after all, such a test is considered no test at all by the originator of the method, but we feel sure that unbiased readers of our report will agree that the test of the enzyme treatment, as carried out at the New York Skin and Cancer Hospital, is an illustration of a "fair test."

In an address on the treatment of inoperable cancer at the International Surgical Conference, Brussels, 1908, Sir Henry Morris [2] said that Dr. Beard originally supported his contentions by two experiments on mice. According to Dr. Beard, two mice suffering from Jensen's carcinoma exhibited symptoms after the injection of 2½ minims of 1.5 per cent. solution of trypsin, which Dr. Beard ascribed to intoxication by the "products of the tumor (an alcohol?), as extracted and digested by the large dose of trypsin." The tumors were found to be in an advanced state of degeneration and necrosis. No

[1] The question has been asked, "Why was the method tested in so many cases?" The answer is twofold: In the first place, through the wide publicity given in the secular press to the "wonderful cures" effected by this means, patients were so insistent upon being treated thereby that their requests were granted. In the second place, Dr. Beard changed his instructions from time to time, necessitating an increased number of cases in order to make the test effectual.

[2] Morris, Sir Henry.—"The Treatment of Inoperable Cancer," Second International Surgical Congress, Brussels, 1908, Vol. II, p. 295.

evidence was advanced that degeneration and necrosis did not occur independently of the treatment. As a matter of fact, ninety per cent. of tumors obtained by propagating Jensen's carcinoma exhibit very extensive necrosis; only a thin shell of healthy tissue may remain.

Mice suffering from adenocarcinoma mammæ, squamous-celled carcinoma, malignant adenoma, and sarcoma, were treated with trypsin in many series of experiments in the laboratories of the Imperial Cancer Research Fund. Attention was paid to any evidence of the symptoms of intoxication, the induction of necrotic degeneration and inhibition of growth, and of the specific action of trypsin on cancer tissue while sparing other tissues, as described by Beard, but his statements were not confirmed.

"The solutions," quoting from Morris, 'employed by them (even when diluted to the strength of one in a thousand and injected subcutaneously into mice in doses of $0^{cc}3$ to $0^{cc}5$) produced great irritation and digestion of the overlying skin, so that in the space of one to three hours after injection the hair over the site of the fluid fell out and a large moist ulcer formed. Hence the doses of active trypsin which it is possible to give to mice subcutaneously without local destruction of tissue, and which are perhaps not inferior to the doses applied to the treatment of the human subject, are so infinitesimal that the absence of influence on the growth of tumors in mice so treated is not astonishing. To meet this objection other methods of application were sought. Intraperitoneal injection is also followed by digestion of the abdominal wall at the site where the fluid collects, the destruction of tissue tending to advance along the tract of the needle used to inject it. In their highest degree the consequences are speedy ulceration of the abdominal wall and escape of the intestines, which appear not to be attacked. Both the above methods of administering trypsin in doses sufficiently great to be effective cause the greatest inconvenience to mice, which suffer obviously from great pain, and have to be quickly destroyed. It was found, however, that relatively enormous doses could be injected directly into the venous system and tolerated without any visible discomfort. A quantity of fluid almost equal to the total amount of blood in a mouse can be so injected, and, weight for weight of animal, doses of trypsin 300 times greater than those advised for administration to the human subject have been introduced into the circulation within a short space of time. The negative results on the growth of tumours bore out those obtained with subcutaneous injection.

"The effect on tumour growth was tested in yet a third way. Mice were treated by the direct introduction of trypsin into the circulation before inoculation with a transplantable tumour, and the treatment continued during the succeeding ten days following inoculation, i. e., till that time had elapsed within which the new tumours usually develop. The treatment was powerless to prevent the inoculated tumour tissue from 'taking.' The results were found to be quite independent of the amount of trypsin injected. The fact that the newly implanted tissue established itself, disposes of the hypothetical objection that the other methods of testing trypsin had failed because the tumour cells had in course of treatment been able to immunize themselves against trypsin. The subsequent growth of the tumours in the mice which had been previously treated and continued to be treated with trypsin showed no differences from that of the tumours in normal animals not treated by trypsin."

The method seemed to offer an unusually hopeful field for legitimate clinical experimentation. The originator of the theory upon which it was based, Dr. John Beard, of the Department of Embryology, University of Edinburgh, brought to the work a scientific spirit, a mind trained in the verification of hypotheses in his own work, and a reputation for earnestness and sincerity of purpose which at once inspired confidence. Not being a doctor of medicine, he had no means at his disposal for testing his theories, and hence he appealed to the medical profession that such a test be made as would prove or disprove the correctness of his hypotheses.

Dr. Beard succeeded in arousing the interest of a goodly number of members of the medical profession, both in Europe and in America, as was shown by the fact that more than one hundred articles had appeared concerning the matter up to the time we began our test, and that five hundred physicians, out of more than three thousand to whom letters of inquiry were sent by me as Secretary of the Department of Scientific Research of the New York Skin and Cancer Hospital, had employed the method in one or more cases.

There seemed quite enough of possible value in the treatment to warrant its trial. Furthermore, through the overzealous influence of certain medical writers for the lay press, and of a few premature enthusiasts within the ranks of the profession itself, the method was heralded far and wide, and patients themselves soon began to make the demand that it be tried in their cases, attesting their willingness to abide by the consequences.

Hoping that it might prove at least a hopeful adjuvant, if not the boon which had been predicted, and believing that it would do no harm, we proceeded with the test in more than one hundred cases, one hundred of which are included in the appended table in the report.

The hospital furnished a sufficiently large number of patients from which to draw the major proportion of the cases in which the treatment was employed. To use it only in advanced, irremovable, and inoperable cases was, perhaps, simple enough; but such cases do not give a sufficient basis for a complete trial. The surgeon, who must look upon the matter, not as a "pure scientist" (quoting a term applied by Dr. Beard to himself), cannot bring himself voluntarily to subject a patient with cancer in an early stage, when the disease is amenable to complete removal (and probable cure) by surgical intervention, to experimentation with any non-surgical agent, no matter upon what scientific basis it may be exploited. Of course, in the judgment of some, certain superficial local growths form legitimate exceptions to this general statement. Such a method, therefore, may be tried in early cases only where, despite the surgeon's earnest advice, operation is positively refused by the patient, or where, for reasons aside from the cancer, it is impossible to operate. Twenty-eight of the one hundred cases treated in the course of the three-year test of the enzyme method were of this character. The majority, however, were in various advanced stages of the disease.

An enormous amount of time and patience, and a goodly sum of money, were necessary in following out the details of the test. Inasmuch as the trial, of necessity, extended over a long period of time, in some cases months, it was not practicable in every instance to care for the patient in the hospital, the individuals themselves not infrequently objecting to being so long away from home. Under these circumstances, when the patient could not afford the expense, it was necessary for us to furnish medical attention and to employ trained nurses to administer the treatment and to carry out the régime in the home after the patient's discharge from the hospital. To follow up the records in all cases, from week to week and from month to month, in such manner as to render possible an accurate report of each, in many instances necessitated tracing the patient from tenement to tenement, sometimes from city to city. Innumerable obstacles were confronted at every turn. We endeavored, however, to meet them as they arose, to follow the régime outlined as closely as possible in accordance with the exigencies of each individual case, and to keep as accurate data as possible in each instance.

In addition to the use of the enzymes, many details of management were urged by Dr. Beard. His various suggestions were executed, and the treatment was carried on with his knowledge and approval throughout.[1] Furthermore, in a certain number of cases a careful study was made of the blood and urine, and microscopical and gross specimens were sent to many pathologists of repute, particularly where there was any doubt as to the diagnosis of malignancy.

The materials employed, for which we were indebted to Mr. B. T. Fairchild, who coöperated with Dr. Beard, were as follows: (1) Holadin capsule, a pancreas gland extract containing all the pancreas enzymes—trypsin, amylopsin, and lipase—and the milk-curdling ferments. This was given to aid digestion. (2) "Pepule" oxgall compound, which contains inspissated oxgall, *extractum pancreatis,* and extract of nux vomica. The object of this was to give tone to the bowel and to aid elimination. (3) *Lotio pancreatis,* a glycerin extract prepared directly from the fresh gland and carrying in solution the entire soluble gland constituents. This solvent of broken-down tissue was applied topically to the ulcerating surfaces. (4) *Injectio trypsini,* a glycerin extract of trypsin which, according to Beard, was supposed to "kill" the cancer cells. (5) *Injectio amylopsini,* a glycerin extract of amylopsin, which was thought to "digest" the dead cancer cells.

The first pancreas injections were made of a proteolytic power equal to two per cent. of trypsin, and had been adopted in consequence of a strength or "percentage" of trypsin, first extemporaneously prepared and used by Beard and others. The medium, 60 per cent. glycerin, had already been found to meet the requirements, containing the enzymes of the fresh pancreas extract in an active and sterile condition. This, however, necessitated preliminary dilution in making the injection ready for use. Experience warranted an increase in tryptic power, and it was found that this desideratum could be achieved only by a more aqueous medium. Accordingly, the proportion of glycerin was reduced to 20 per cent. This lower content of glycerin afforded the advantage of increase of trypsin content and increase of dosage, as found in the ampoule.

The various injections of trypsin furnished for our use were identified for convenience of record as follows: "Regular," 60 per cent. glycerin, equal to 2 per cent. trypsin (dry); "Fortified," 60 per cent. glycerin, double strength of the "Regular";

[1] Dr. Beard (*op. cit.*, pp. 180-181) says he was "entirely ignorant of his (the author's) doings," with the exception of one of the earlier cases. My personal visits to his home, my numerous written communications from him, all of which are on file, and the history card of a patient referred to me by him, show that Dr. Beard's memory is at fault in this matter.

"Special," 20 per cent. glycerin, double the strength of the "Regular"; "Special XX," 20 per cent. glycerin, four times the strength of the "Regular" (this was used in most of our cases); "Special Quadruple X," 20 per cent. glycerin, six times the strength of the "Regular" (prepared especially for this test, and said at the time to be the strongest it was possible to make).

Injections of amylopsin of corresponding strength were furnished. The 20 per cent. glycerin amylopsin injection presented parallel advantages with the 20 per cent. trypsin injection, in increased potency, and in available volume of dosage without dilution. Thus twenty minims of the 20 per cent. glycerin "Special" carried an enzyme potency corresponding to a sixty-minim injection composed of twenty minims of 60 per cent. glycerin solution from an ampoule, with forty minims diluent—sterilized water.

Having noted the strength of the injections, it will be seen from the cases detailed later, how much stronger were the injections used in many of our tests than were those employed in the cases reported by a number of writers during the earlier months of the history of this method. The idea entertained by many at first, to the effect that only moderate doses of weak solutions of trypsin could be tolerated, was proved entirely erroneous in our experience. In many cases we were able to give daily two or three ampoules (twenty minims each), and in several instances, one hundred minims of the "Quadruple X" solutions were given for days at a time with no untoward effects.

From the above it will be seen how absurd were some of the earlier claims of "cures," as well as some of the reports of unusual symptoms and "terrific" results noted from the small doses employed.

From this trial the following conclusions were drawn:

(1) That the internal medication with holadin and oxgall aided digestion and increased elimination.

(2) That *lotio pancreatis* applied locally cleaned the ulcerating surface by removing organisms, thus aiding in diminishing the absorption of their products.

(3) That aiding digestion, increasing elimination (by skin, kidneys, and bowels), and increasing local absorption, were the most important features of the treatment.

(4) That the régime, by increasing resistance, seemed, in some cases, to decrease the rapidity of the malignant process.

(5) That control cases given injections of glycerin and water, or sterile water alone, plus the régime, fared as well as did those on the full enzyme treatment.

(6) That *injectio trypsini,* in some cases, seemed to cause more rapid disintegration of cancerous tissue—to "liquefy" it, according to Beard.

(7) That, while it seemed to accelerate the breaking down in the center of the tumor mass, the periphery was found to be actively growing, as was true of Case VII (Case I, of Dr. W. J. Morton's published series). When injected into the tumor itself this disintegration was more marked.

(8) That because of the tendency of the *injectio trypsini* to disintegrate the tissues, it may be a direct menace to life (a) by eroding large blood vessels (when the disease is contiguous to these structures, as when deep in the neck or in the pelvis), thus causing death from hemorrhage; (b) when given in large doses, over considerable periods of time, by overwhelming the system with toxic products (tumor toxins), thus, in some cases, hastening death.

(9) That the injections were often painful, and patients many times refused to take them.

(10) That the so-called "trypsin abscess" proved, upon examination of the material, to be unabsorbed *injectio trypsini* plus broken-down tissue.

(11) That when real abscesses formed they were due to faulty technic, to localization of a general sepsis resulting from the absorption of toxic products, to an accompanying sepsis of whatever origin, or to a complicating acute infection.

(12) That *injectio amylopsini* seems to diminish cachexia in some cases, in accordance with the claims of Beard and others.

(13) That in some cases there was no reason to believe that *injection amylopsini* exerted the action claimed for it.

(14) That when amylopsin was injected directly into the indurated area left after injecting trypsin, absorption of the trypsin solution was not hastened.

(15) That 100 minims daily of the "Quadruple X" solution, the strongest made, was given in some cases with no untoward effects.

(16) That improvement in hemoglobin (5 to 12 per cent.) during the first few weeks of trypsin treatment, occurred in about one-sixth of the cases examined. In only one-third of these was the increase ascribable to the trypsin alone.

(17) That in a few of the cases a gradual and moderate increase in the number of polymorphonuclear neutrophile cells was noted during the first two weeks of the trypsin treatment.

(18) That, with the exception of two cases, such leukocytosis as was noted was attributable to the occurrence of

complications during the first two weeks of trypsin treatment.

(19) That in fifteen out of twenty-two cases above mentioned, a steady increase (6 to 12 per cent.) in number of eosinophile cells was noted while patients were on the trypsin injections. There was no eosinophilia in the control cases, nor in the cases treated by trypsin given by mouth.

(20) That eosinophilia occurred regularly in cases of carcinoma involving the bones or the intestines, even without the exhibition of trypsin.

(21) That the claims for eosinophilia as a test have not been substantiated in our experience.

(22) That in two cases albumin and casts were found in the urine before treatment was begun. In neither of these was the amount of albumin or the number of casts increased at any time throughout the continuation of the trypsin injections.

(23) That in severe cases in the very last stages of the disease, hyaline, granular, a few pus casts, and occasionally albumin made their appearance.

(24) That in two other cases in which it was impossible to obtain specimens of urine before beginning the treatment, albumin and casts were present when the cases came under examination; and as the trypsin doses were increased the amount of albumin and the number of casts were increased.

(25) That dextrose was at no time found in any of the urine specimens examined, not even when untoward manifestations of trypsin were present and large doses of amylopsin were being given.

(26) That the series of experiments which were conducted for the purpose of ascertaining the presence or absence of an enzyme in the urine, with properties of digestion similar to trypsin, showed the presence of such an enzyme body (irregularly present) in (a) trypsin-treated cancer cases; (b) non-cancerous untreated cases; (c) cancer cases which had not received the trypsin treatment.

(27) That the exact potency of this enzyme body in the urine with reference to the treatment was not ascertained. No enzyme body was found in urines in which there was ammoniacal decomposition.

(28) That the enzyme treatment as administered in the cases herewith reported, and according to the suggestions of Dr. Beard, plus important details of régime, does not check the cancerous process.

(29) That it does not prevent metastasis.

(30) That it *does not cure cancer.*

The test was a negative one, unfortunately, but it should serve the purpose, with both the medical profession and the public, of illustrating the thorough, exhaustive, scientific tests to which reasonable measures are subjected in the effort to find non-surgical methods of treating cancer.

Other hospitals and research centers have been equally willing to give a fair trial to any method which has answered scientific requirements, even to a partial degree. Notable instances of this are the Imperial Cancer Research Fund; the Middlesex and Cancer Hospitals, London; the Cancer Hospital, Heidelberg, and the Cancer Pavilion of the Charité, Berlin.

In the pages which follow are recorded illustrations of "fair tests" applied to other measures which from time to time have been proposed for the treatment of cancer.

SERUM FROM BIRDS OF PREY

In 1904, two accredited physicians, with European training, presenting letters of introduction from the Commissioner of Public Health of New York City, and from well-known physicians, requested the writer to test a serum which they claimed to be a cure for cancer. The serum was made from birds of prey to which cancer tissue and cancer juice had been fed for months, which had then been killed, and from which the blood serum had been obtained. This was injected into the subcutaneous tissues of the subject being treated, not into the cancer area.

After duly weighing the evidence presented, it was decided to test the agent. This was done systematically, according to the suggestions of the originators, in some fifteen cases. The serum was applied by the doctors, who had taken a small place in the country where they kept the birds from which the serum was obtained.

There were periods of apparent improvement, lessening of pain and other symptoms, but it was soon realized that these remissions of symptoms were nothing more than could be accounted for by the psychic effect of the new hope which a new remedy always inspires for a time. After satisfying ourselves fully that this was true, and seeing no real benefit in a single case, the treatment was abandoned. So far as I am aware nothing has ever been accomplished by means of this serum.

"CANCROIDIN," "ANTIMERISTEM"

(The Otto Schmidt Serum or Vaccine)

The Schmidt serum or vaccine affords an excellent illustration of the willingness of individual physicians, cancer hospitals, and research institutions to test a proposed new method of treatment which has a seeming foundation in scientific theory or principle.

The Schmidt "cure," like a number of apparently scientific methods, was based upon the supposed discovery of the cause of cancer. Schmidt claimed to have isolated and cultivated a cancer parasite, from which the proposed serum was prepared by two methods.

By the first method, cultures were made of the parasite, these were sterilized, and from them a pure "killed culture" was obtained. This was injected subcutaneously in small but increasing doses.

According to the second method, an animal was inoculated with increasing doses of the "cancer parasite," and from the animal a serum was obtained. This was injected subcutaneously into the subject to be treated.

The method was first announced to the English medical world in a paper read by Dr. Josse Johnson before the Abernethian Society of St. Bartholomew's Hospital (a students' medical society), November 5, 1905. Dr. Johnson made for Dr. Schmidt, the announcement of the discovery of the parasite, of the preparation of the "killed culture" and the serum, and of the successful treatment of twenty-nine cases.

Despite the fact that the proposed "cure" had been announced with a decided suggestion of secrecy, the Middlesex Hospital, London, under the direction of J. W. Glenton Myler, Registrar to the Cancer Wing,[1] decided to investigate the method, both as to its curative properties and its diagnostic value.

Nine patients in the cancer wards of the hospital, with their consent, were subjected to the treatment, the selection of suitable cases having been made by Dr. Johnson and the hospital medical officers. Dr. Schmidt visited the hospital during the test and expressed himself as being satisfied with the cases.

In every detail the test was conducted with perfect fairness to the originator of the method. Photographic and other records of the cases were carefully kept, and the treatment

[1] Archives of the Middlesex Hospital, Vol. III, Third Report from the Cancer Research Laboratories.

was administered in accordance with Dr. Schmidt's directions, the injections throughout being made by his friend and champion, Dr. Johnson.

Instead of proving to be a cure, the method was of no benefit in any case. Its diagnostic value was *nil,* no case of undoubted cancer showing the slightest temperature reaction, as it was claimed would be the case. The most that could be said of the treatment in the Middlesex report was that it at least did no harm, since it in no way modified the course of the disease.

Despite the objections and protests of the medical profession of Germany, the method continued for a time to receive more or less notice in the medical and secular press.

Later "Cancroidin" appeared in print under the name "Antimeristem," and numerous reports have appeared in medical literature relative to this agent, prepared from cultures of Schmidt's *mucor racemosus malignus.* According to Johannsen,[1] aside from a few cases reported by Schmidt[2] himself, practically all the published cases concern *improvements,* but not *cures.* In numerous instances in which the method was employed, no favorable influence was reported. Kolb,[3] for example, holds that Schmidt's "Antimeristem" exerts no specific effect of any kind upon the tumor, merely giving rise to a reaction in the inflamed vicinity.

Aside from furnishing an excellent illustration of the willingness of the medical profession and of research institutions to give a fair trial to a proposed remedy for cancer, the variously named Schmidt method affords an illustrating example of the commercial aspect of many of the alleged "cures" for this disease. The following advertisements, of recent appearance, translated verbatim, need no comment:

"VACCINE-THERAPY[4]

"For Malignant Tumors

"The great efficacy of the Vaccine *Antimeristem-Schmidt* in carcinoma and sarcoma is shown by hundreds of reports, from university clinics, large hospitals, and medical practitioners.

"Indications: In obscure cases, for the confirmation of the diagnosis; after radical operations, for the prevention of recurrence; after

[1] Johannsen.—"Ueber drei Verreuhe der Behandlung inoperabler Karzinome mit Antimeristem," *Centralblatt für Gynäkologie,* 1912, Vol. 36, No. 14, p. 426.

[2] Schmidt, O.—"Die Wirkungsweire des Antimeristem bei der Krebsbehandlung," *Zeitschrift für aerztliche Fortbildung,* No. 21, 1911, p. 649.

[3] Kolb, K.—"Ein Beitrag zu den Misserfolzen mit Antimeristem (Cancroidin-Schmidt)," *Münchener med. Woch.,* 1911, p. 1076.

[4] Advertisement on title page of *Ars Medici,* January, 1912.

partial operations, for the supplementing of the result; in all cases which for some reason are inoperable (primary tumors, recurrences, and metastases).

"*The preparation is dispensed only on professional prescription.*

"Directions for use, in German, English, French, Italian, Russian, Spanish, Swedish, and Norwegian.

"Literature in several languages may be obtained through the undersigned firm.

"General Deposits in all countries.

"Sole Manufacturer: Bacteriologico-Chemical Laboratory,

"WOLFANG SCHMIDT,

"Cologne, Germany."

"IN DEFENSE AND FOR INFORMATION [1]

"In the course of the last months the daily papers have repeatedly published articles from the pens of experts, dealing with the problem of the present status of cancer treatment.

"*The Present Status of Cancer Treatment*

"All those procedures are enumerated therein which at some time, in animal experiments or clinical cases, have shown an *influence* upon the *cancer tumors.* But *the* procedure which has accomplished by far the *largest number of cures,* and moreover in the *most malignant and serious cases,* in contradistinction from other measures,—this procedure they are endeavoring to hush.

"*To Hush Up*

"We are referring to the treatment which was introduced into practice and perfected into a system by Sanitätsrat [Health-Councillor—an official title] Dr. O. Schmidt, of Cologne, being a treatment with his vaccine, 'Antimeristem,' which is manufactured by the undersigned. In the past year, Dr. O. Schmidt was enabled to report 40 cures of cancer, and 304 improvements, in part approaching to a cure. At the present writing these figures have increased by 13 cures and 143 improvements, so that the total result amounts to 500 cases.

"It can be positively assumed that about the same number of cures and improvements have *not* been published in medical journals, and have *not* come to the knowledge of the undersigned. This conclusion is based upon the fact that physicians, in reordering the preparation, frequently mention a cure which they obtained in previous years.

"Only a small minority of the patients have been treated by Dr. Schmidt, by far the majority having been under the treatment of other *registered* physicians, at home and abroad. It seems necessary to make special mention of this fact.

"Among those who have reported favorable results are many professors and directors of university clinics, and large hospitals, the principal contingent being represented by general practitioners. The reports of these representatives of medical knowledge have either not been read, or are intentionally disregarded. Would any one dare to declare them as the mental products of incapable persons, or as voluntary misstatements?

"Dr. Schmidt's publication of last year, referred to above, is concluded in the following words: 'I hope that at last there will be an end to the assertion, made by the competent as well as the incompetent,

[1] Advertisement in *Berliner Vossische Zeitung,* 1913.

to the effect that as yet no carcinoma has been cured by Antimeristem; otherwise, I would have to accuse the originator of a similar assertion as being guilty of an *advisedly uttered untruth.*'

"An assertion of *this* kind has not been propounded since that time; for there are other means by which they hope to accomplish their object, namely by keeping silence and hushing up the facts of the case.

"It is far from the intention of the undersigned to proclaim in the daily newspapers the value of Antimeristem, which moreover is only distributed on a physician's prescription. But he demands *equal rights* for all, and, as this principle is being violated over and over again, in a matter of *such eminent importance,* he now seeks publicity.

"BACTERIOLOGICO-CHEMICAL LABORATORY,

"WOLFANG SCHMIDT, COLOGNE."

The important aspects of these advertisements are not only their direct appeal to the public, and the usual insinuation, openly expressed, that the alleged remedy is being wrongly boycotted by the profession, but also the fact that they were published in 1913, after numerous papers had shown that the treatment was valueless. An article by Jensen [1] was translated into English, and apparently was still being spread broadcast in 1913, although Dr. Mamlock, of Berlin, showed [2] that the case therein cited could not be used to support Schmidt's "Antimeristem" treatment, because a complication with syphilis was almost certainly present. This possibility was also admitted by Jensen.

Doubts are awakened by all the other alleged cures of which reports have been accessible to the author. Two cases of cancer of the tongue, recorded by Aly,[3] continued to grow without the slightest sign of healing, in spite of Antimeristem treatment. No benefit whatsoever was obtained in a case of rectal cancer shown to the Medical Society of Zwickaw in Saxony. Professor Kummel, Director of the Surgical Klinik in Hamburg, proved [4] that a case claimed as a cure of cancer of the palate was not cancer at all. Johannsen obtained absolutely negative results from uterine cancer.[5] An exhaustive investigation of Schmidt's claims was made in Czerny's Institute in Heidelberg by Werner,[6] who recorded uniformly unfavorable results. Editorial comments directed against the use of Antimeristem and its advertisements appear in the same leading German medical journal.[7]

1 Jensen.—*Deut. med. Woch.*
2 Mamlock.—*Zeitschr. f. ärztliche Fortbildung,* No. 22, 1911.
3 Aly.—*Deut. med. Woch.,* 1910, p. 1885.
4 Kummel.—*Deut. med. Woch.,* 1912, p. 1607.
5 Johannsen.—*Deut. med. Woch.,* 1912, p. 819.
6 Werner.—*Deut. med. Woch.,* 1912, p. 826.
7 *Deut. med. Woch.,* 1912, p. 1295, and 1913, p. 951.

It is evident that "Antimeristem" has been tried, and tried fairly. The effrontery with which it is still advocated and advertised to-day is sufficient evidence of the confidence with which the suffering and the weak are appealed to and urged to undergo a course of useless, if not harmful, treatment, with an agent which costs something like four hundred dollars, or eighty pounds, according to the pamphlets and circulars issued by the vendors.

DOYEN'S SERUM

Another of the seemingly scientific "cures" for cancer which has been subjected to the crucial test of scientific investigation is Doyen's serum, so widely heralded a few years ago, and still put forward to-day.

In 1886 Doyen presented before the Academy of Science at Paris his first report of his observations concerning the presence in malignant and non-malignant growths of small, spheroidal, mobile bodies which he thought to be micro-organisms. In 1901 he corroborated these observations in a report to the Academy of Medicine in Paris. In 1903, before the Surgical Congress of Berlin, he further substantiated his previous reports, and made the additional claim of having isolated a micro-organism from both malignant and non-malignant tumors. He gave to this organism the name *Micrococcus neoformans,* and claimed that, inoculated into animals, it had given rise to neoplastic formations.

Doyen believed infection of the body with this *Micrococcus neoformans* to be the cause of the development of new growths, such infection being comparable to that of tuberculosis and actinomycosis.

The outcome of this claim was the preparation of an anti-cancerous vaccine, made by attenuating and increasing the virulence of the organism, and of an antitoxic serum, made from the horse by means of the toxins of the *Micrococcus neoformans.*

These agents, in combination with surgical procedure, were employed successfully, according to Doyen, in 21 out of 126 cases of malignant and non-malignant growths which he reported, in 1904, before the Academy of Science in Paris. The next year he detailed [1] 42 "cures" out of 116 additional cases.

Naturally this "discovery" was immediately heralded all over the civilized world, the secular and medical press devoted a great deal of attention to it, and many cancer patients demanded its trial.

[1] Doyen.—"Étiologie et Traitement du Cancer," Paris, 1905.

While interest in the method was at its height (which, it may be recalled, was coincidental with the height of the interest in the parasitic theory of the cause of cancer), the authorities of the Brompton Cancer Hospital, London, requested that inquiry be made into the treatment of cancer by means of this serum. Accordingly, Dr. Alexander Paine and Dr. David J. Morgan were appointed to make the investigation and to study the presence of the *Micrococcus neoformans* in malignant and non-malignant growths.

The results of the investigation were presented before the Royal Medical and Chirurgical Society of London, March 27, 1906.[1]

Doyen supplied the hospital with vaccine and serum, with which 9 cases of malignant disease were treated, most of the cases having been seen by him and pronounced suitable for the method. In each instance his serum was used alone, that is, without surgical or other treatment, in order that the effect of the agents might not be obscured.

The method consisted in the injection, deep into the muscles of the buttock, at stated intervals of time, of 10 c. c. of the serum or vaccine. In 2 of the 9 cases there was no local change in the growth. In the remaining 7 there was no constitutional reaction, in 2 there was marked increase of pain, and in the remaining 3, cardiac failure, with collapse in 2 cases. No benefit was noted in any case further than the temporary relief of pain, which, as is well known, varies considerably under any circumstances.

The investigation as to the presence of the *Micrococcus neoformans* is discussed under Etiology, Section IV, Chapter 1.

CHIAN TURPENTINE

(Pistacia Terebenthus)

Chian Turpentine, given internally, and by injection, furnishes an excellent illustration of the recurring use of a given agent in the treatment of cancer. It was first used, apparently, by Clay,[2] of Birmingham, England. Immediately following his favorable report, it was tried during a number of months by Hulke [3] at the Middlesex Hospital, and an unfavorable re-

[1] Trans. of the Royal Medical and Chirurgical Society, London, 1906, Vol. LXXXIX, p. 707.

[2] Clay, J.—"On the Treatment of Cancer," 1882. See also: *Lancet,* 1880-1887.

[3] Hulke, J. W.—"Memorandum on the Results of a Trial of Chian Turpentine as a Reputed Remedy for Cancer of the Female Genital Organs, made during several months in the year 1880, in Whitbread Ward, Middlesex Hospital," *Lancet,* London, 1881, I, p. 1019.

port rendered. Despite this discrepancy in the findings, it has continued to be used from time to time, until within the last few years, when it seems to have been finally abandoned. Judging from other instances, however, it is apt to appear in the archives of cancer literature at any time.

Clay gave it internally, and claimed great success from its use. Hulke said of his experience: "The result of this trial completely demonstrated to my own mind that Chian Turpentine is thoroughly useless as a remedy for cancer, whether of the female generative organs or of other parts. It was administered during several months to several suffering from uterine cancer, which, in spite of it, continued its fatal course. In not one case did the vaginal discharge assume the thick, ropy character mentioned by Prof. Clay. As a reputed anodyne it failed to lull pain, and during its use opium was found indispensable. With respect to its alleged hemostatic powers, hemorrhage occurred as frequently and as copiously in women taking the turpentine as in others to whom it was not given."

Despite this unfavorable report it was again used in the Middlesex Hospital many years later.[1] A patient with carcinoma of the cervix took it, in dessertspoonful doses, three times a day, regularly every day for nine months, during which time the disease steadily progressed.

Shaw-Mackenzie[2] first used Chian Turpentine internally in 1891, but later began to employ it hypodermatically, claiming good results.

From the sum total of evidence it may be justly concluded that Chian Turpentine offers no hope of cure, and little if any benefit as a palliative measure.

SODIUM OLEATE (Soap Solution) AND OX-GALL

John Holden Webb,[3] of Melbourne, Australia, claims to have cured cancer by means of injections internally of cholesterin in soap solution and ox-gall ("animal gum"). The theory upon which this practice is based is as follows: "Cancer is uncontrolled cell proliferation due to the deposition of cholesterin, from the cell, either locally, from injury, or dependent on some chemical change in the liver secretion, associated with deficiency of the bile-salts which normally hold cholesterin in solution." Webb found that salt solution offered the best

[1] Myler, Glenton.—Archives of the Middlesex Hospital, 1904, Vol. II, p. 65.

[2] Shaw-Mackenzie.—"The Nature and Treatment of Cancer," 1905.

[3] Webb, John Holden.—*Lancet*, October 12, 1901, p. 976.

medium for the cholesterin injections. After some disappointment with the method, Webb omitted the cholesterin and used merely injections of superfatted soap in conjunction with the internal administration of ox-gall.

Shaw-Mackenzie[1] reported some successes with this method, and from time to time other more or less desultory reports of its use have appeared in medical literature. None of these, however, has been sufficiently definite and convincing to give it a permanent place in the medical treatment of cancer. Personal correspondence with Dr. Webb failed to give me enough evidence of the usefulness of the method to warrant its trial. Recent instances of its use have come to my notice, however, and without doubt history will repeat itself with this agent.

MOLASSES

Two cases of cancer were reported in the *Mackay Standard*, Queensland, Australia, in 1902, as cured by the use of molasses. This report attracted considerable attention at the time, and while the diagnosis of the cases was questioned, the method was tried at the Middlesex Hospital.[2] Several cases of cancer in different parts of the body were treated.

According to the first reports, the molasses was given internally, commencing with one dram and increasing to two ounces. It was given in milk or water, on an empty stomach, four times daily. The molasses employed was from cane sugar, pure and unrefined.

In the Middlesex Hospital test it was administered locally as well as internally. Ulcerated breasts were dressed with it, and tampons soaked with it were introduced into the vagina and brought into contact with the ulcerated surface in cancer of the cervix. Ulcerated surfaces were kept clean, but no tendency to heal was noted. It lessened the fetor of uterine discharges, but did not affect the amount of the discharge.

Results were not sufficiently favorable to warrant a continuance of its use, and nothing is now heard of molasses in the treatment of cancer. This seems to be one of the few instances in which the test sufficed to check the employment of an apparently inefficacious agent.

1 Shaw-Mackenzie.—"The Nature and Treatment of Cancer," 1905

2 Archives of the Middlesex Hospital, Vol. II, 1904, p. 93.

VIOLET LEAVES

In 1901 a paragraph went the rounds of the press [1] describing the "cure" of a tumor of the tonsil by the application of a number of fomentations made from an infusion of green violet leaves. The diagnosis of cancer had been "made certain by microscopic examination of a small portion removed." The patient, in gratitude for her recovery, had some leaflets printed describing the mode of application of the remedy. This use of the violet leaf furnishes an excellent illustration of the persistence from the past to the present of empirical methods of treatment.

The violet leaf, according to the *Lancet,* figures not infrequently among the recipes of the old Anglo-Norman writers whose manuscripts are preserved in the British Museum. The pansy (*Viola Tricolor*) possesses cathartic and emetic qualities. "The dog violet is vaguely recorded in an old edition of Balfour's 'Botany' (1854) to have been at some time or other prescribed for 'skin diseases.' In the days of the Plantagenets, monkish medical writers treated most diseases with the violet, whether dog, pansy, or sweet March they do not state."

"The green leaves were used with other herbs to make plaisters and poultices for inflammations and swellings," according to "The English Physician," *Reissus*—1792, of Nicholas Culpepper.

Following the revival of 1901, the treatment of inoperable cancer by means of the extract of violet leaves was heralded in the secular press in 1903. The first case reported at that time was one of "cancer of the mouth." The diagnosis, unlike the one in 1901, was not confirmed by microscopic examination, but was certified by competent physicians. The daily press exploited the case as one of "cure," and for a time violet leaves were in demand, and much valuable time was wasted with this method of "tampering."

The extract was employed locally, by means of lint or gauze soaked in the fluid and applied to the diseased surfaces. This dressing was changed two or three times a day, according to the amount of discharge. In cancer of the cervix, vaginal tampons soaked in the extract were employed.

The Middlesex Hospital [2] tried the method in a number of cases on two occasions. In the first report it was stated that in no single case did any good result from the method. There were no relief from pain, no lessening of discharge, no abate-

[1] *Lancet,* editorial, November 23, 1901, p. 1430.

[2] Archives of the Middlesex Hospital, Vol. II, 1904, p. 91; also, Vol. IV, 1906, p. 75.

ment of other symptoms. In one case of cancer of the breast there was an increase of fetor.

In the second report, of twelve cases subjected to the treatment, two cases, it was stated, were discharged at their own request, their condition being unaltered; six cases died, and in the remaining four, which were still under observation when the report was published, the disease was steadily pursuing its normal destructive course. In no case was a beneficial result obtained, although temporarily the surfaces of ulcers were cleaned as the result of the moist application.

THE INVESTIGATION OF "QUACK CURES"

In the preceding pages we have discussed the testing of such proposed methods of treatment as have a more or less plausible excuse for their existence in the apparently scientific basis upon which they are evolved. There is another class of "cures," however, which the medical profession is importuned to employ, sometimes to test thoroughly, which has no excuse for existence save the greed of the originators or the blind faith of their victims. Yet some even of these have been tested in a scientific and serious manner by members of the profession, some have been investigated by legislative bodies, and others have been exposed to the searchlight of truth by medical and secular journals. It is the purpose of the next few pages to give in brief detail the history of some of these investigations.

THE MATTEI "ELECTRICITIES"

One of the most remarkable instances of the investigation by the medical profession of a "quack cure" for cancer is that of the so-called Mattei method, the "electro-homeopathic system," the "new medical science."

Count Mattei and his remedies were first brought prominently before the notice of the English-speaking world through an article by Lady Paget, which appeared in the *National Review* in May, 1890, and later by an article by the late W. T. Stead,[1] editor of the *Review of Reviews*.

[1] Stead, W. T.—"Can Cancer Be Cured? A Visit to Count Mattei: His Challenge to the Faculty. With Letters from Prof. Huxley, Prof. Tyndall, Sir Morell Mackenzie, Prof. Ray Lankaster, and Others," *Review of Reviews*, January, 1891. See also:

Mattei, Cæsar.—"Electro-Homeopathy. The Principles of a New Science, Discovered by Count Mattei of Bologna," 1880.

Kennedy, S.—"Is Cancer Curable? The Cancer Controversy: Mattei v. the Knife; how it began, how it ended; with an epitome of Mattei treatment of cancer and general diseases," London, 1891.

The latter article sets forth the whole story in so interesting a fashion that we quote from it freely. It gives so plainly the attitude of a large part of the public, even of the most intelligent public, concerning the efforts of the medical profession to solve the cancer problem, that it "points a moral and adorns a tale."

"Can cancer be cured?" is the opening question. "According to the doctors," Mr. Stead continued, "it is incurable. Cut it out when it first appears, and you may have a chance. Let it alone, and you will die in agony. Medicine can do nothing, but one can administer a drug to dull pain; the knife at the beginning and morphine at the end—these are the Alpha and Omega of medical science in dealing with this deadly disease. Count Mattei asserts that cancer can be cured—that he has cured it, and is curing it, and he challenges scientific examination. That challenge must be taken up, and in the following article, I venture to hope the case is so stated as to render it impossible any longer to refuse the inquiry for which the Count pleads."

"Count Mattei," continued Mr. Stead, "is the Italian nobleman whom Lady Paget visited after his medicines had cured her husband, now his Majesty's Ambassador to Vienna. It was her paper in the *National Review,* of May, partially reprinted in these pages, that first drew general attention to the fact of his existence, although a short time previously Commissioner Booth-Tucker had spoken of his medicines. Commissioner Tucker, when returning from India by the Brindisi route, passed the Count's castle at Riola, called upon him, was very favorably impressed with the Count's personality, and came away believing almost as much in Count Mattei as he had previously learned to believe in the Mattei medicines."

The fact that Commissioner Booth-Tucker had been cured by the Mattei medicines of a chronic dysentery which had baffled the Anglo-Italian medical profession for years, did not especially interest Mr. Stead, and it was only after the appearance of Lady Paget's article, which was emphasized by a second from the same pen, that the editor of the *Review of Reviews* began to take a keen personal interest in the Count and his medicines. "For," as he said, "this was not the testimony of a nobody. It was published evidence of a lady whose husband has achieved the highest position in the diplomatic service—a lady, moreover, who could not possibly have any personal or interested motive in recommending the remedies to the world. There was, of course, the usual condemnation pronounced by the orthodox faculty. Without that, no new discovery can be deemed worthy of notice by the outside public. Such censure indeed is the *prima facie* intimation that there may be something in it."

According to Lady Paget and other creditable witnesses, this "philanthropic Italian noble" had discovered certain remedies which she declared to possess an almost supernatural efficiency for curing disease incurable by the aid of the physician. "And not one of all the Faculty," said Mr. Stead, "deemed it worth while so much as to inquire whether or not these things were so."

Shortly after his interest had been thoroughly aroused in the "electro-homeopathic" system of medicine, Mr. Stead visited Mrs. Booth, wife of the late founder of the Salvation Army, who was at that time upon her death bed, the victim of cancer. "We talked much," he continued, "of cancer and the possibility of its cure. Mrs. Booth told me that one of the saddest thoughts which darkened her closing hours, was that the long course of experiment to which she had permitted herself to be subjected had not resulted in the discovery of any sure mode of treatment that could cope with this terrible scourge. . . . 'What,' said I, 'of the Mattei treatment?' 'His is the best,' she said emphatically. 'His green "Electricity," what would I have done without it? I have constantly applied it, and it alone has given me any relief from this terrible pain.' 'But,' said I, 'his treatment did not cure you.' 'No,' said she, 'it did not; but that is because I did not stick to it. It is so slow and tedious to be always taking these little sips, and after a time I gave it up.' "

When Mr. Stead reminded her that her family considered the remedies to have been thoroughly tested in her case, she emphatically assured him that she was dying, not so much because of the cancer as because she had neglected to use the Mattei remedies. She believed that if she had persisted in their use she might have lived many years. So great was her confidence in the remedies that she made her children promise her that if they were attacked by the disease which was about to carry her off they would go to Count Mattei and place themselves under his treatment.

This incident seemed to deeply impress Mr. Stead, and he began his investigation into the method. In Lady Paget's article reference was made to a physician who practiced successfully in London with the Mattei remedies. Mr. Stead called upon the gentleman, who assured him that what Lady Paget had said was true. Shortly after this the doctor reported to Mr. Stead a case of malignant cancer cured by the use of the Mattei remedies. He promised to have the patient come from Scotland to London, and to submit the patient and her history to Dr. Herbert Snow, of the Cancer Hospital, and any committee of experts whom he might select from the medical faculty.

So impressed was Mr. Stead by all this evidence that he immediately made a visit to Count Mattei in his castle, La Rochetta, in Italy. From the Count, who was then eighty-two years old, he learned the following story of the "wonderful discovery":

When Parliamentarism gave way to Revolution in Italy, Count Mattei gave up the political life of which he had been a part, and devoted his life to the study of agriculture, botany, and chemistry. The discovery of his remedies was directly traceable to his observation of the successful efforts of a shepherd dog to cure himself of a loathsome mange by means of an herb. The Count gathered some of the leaves of the plant, distilled them, and tried the product on a patient suffering from scrofula, with wonderful results. By degrees he succeeded, according to his story, in compounding eight or ten medicines and five "electricities," with which he treated all manner of diseases, cancer among the number. He was a follower of Hahnemann, except that he believed in combating the causes of disease rather than its outward manifestations. Mr. Stead did not seem to be impressed with the absurdity of this statement from one who had had no medical training.

With all earnestness Mr. Stead continued his account: "His herbs are good, no doubt; but the grand secret is the fixing in the remedy of a mysterious something which he calls the electrical principle. This, he asserts, is the vital principle of the universe, and, as far as I could make out, is cousin-german to the astral fluid of the occultists, or the strange etheric force of Keeley. Count Mattei, however, knows nothing of the astral force, or of Keeley's motor. He maintains that he knows how to make herbal decoctions instinct with a potent, vital, electrical force which enables them to work wonders."

Pope Pius IX, according to the story, had placed at the Count's disposal a part of the hospital of St. Teresa in Rome, where he is said to have achieved some marvelous cures of cancer in an incredibly short time. That was back in the sixties and seventies. He is said not to have sold his remedies at that time, but to have given them to anyone who asked. He had also opened a dispensary in Bologna, where, from 1865 to 1867, he claimed to have cured an immense number of people. The

"Regular Faculty" was hostile to him. He appealed to the Church to add the healing of bodies to the healing of souls, and to arm every parish with the cheap and efficacious remedies which his discovery placed within their reach. He issued a circular to this effect to the ministers of all religions, but received no response.

The hostility of the orthodox medical profession, together with threats of personal violence, led the Count to seek the seclusion of the fortress of La Rochetta, where Mr. Stead found him.

In time the modern medical laws of Italy had prohibited the Count from practicing the healing art, inasmuch as he held no medical diploma; and another law, passed about the time of Mr. Stead's visit to the Count, prohibited the sale in Italy of a remedy the nature of which was not sufficiently stated.

The excuse which Count Mattei made for not giving to the world so beneficial a secret, was the usual one—that he could not be sure that others would manufacture the compound with the care and exactitude upon which its effect depended.

From the distributing office in Bologna it was said that about a million phials of the little granules were sent out every year, and as many bottles of the "electricities," and boxes of the ointment. These went practically all over the world. The Matteiists published monthly and fortnightly bulletins of the "electro-homeopathic system," which also had a very wide distribution.

"It was curious," said Mr. Stead, "to hear the Count talk of cancer cures as if they were among the ordinary every-day incidents of life." "Imagination will not cure a cut, nor will imagination cure a cancer," yet the Matteiists claimed to do both. It would seem, however, that even the imagination of a "high potency" Hahnemannist could hardly be equal to conceiving of a malignant cancer being influenced by a pin-head granule of one of the Mattei "electricities" dissolved in a glassful of water, a teaspoonful of this taken, the rest thrown away, this spoonful mixed with another tumblerful of water, a spoonful of this last glassful taken, the rest thrown away, and this spoonful mixed with another glassful of water, the last being sipped by the patient afflicted with cancer. And yet such was the remedy which the Matteiists and their followers challenged the medical profession to test!

Full of enthusiasm, Mr. Stead returned to London, bent upon forcing the medical world to recognize the wonderful discovery of this Italian Count. Two cases of sarcoma, so pronounced by pathological report, which had been cured by the "electricities," clinched his determination. After collecting what he considered sufficient evidence, Mr. Stead addressed to the medical profession a letter asking that a scientific test and investigation be made. In the article from which we have quoted, some of the replies are published. It was left to Sir Morell Mackenzie, however, to make a suggestion which met with Mr. Stead's approval. It was to the effect that a committee be appointed for the purpose of investigating the matter, and that a small hospital be opened for receiving the patients to be treated. He volunteered to serve as a member of the committee.

Inasmuch as certain regular practitioners of medicine had begun to employ the method, and as its cause had been championed in the public press by such prominent persons as Lady Paget and Mr. Stead, it was deemed a public service to bring to light the true character of the treatment. To this end, following the suggestion of Sir Morell Mackenzie, the Mattei Investigation Committee was formed.

The members of the Committee were Sir Morell Mackenzie, Mr. Lawson Tait, and G. W. Potter. After the death of Sir Morell Mackenzie, Mr. H. A. Reeves, F.R.C.S.E., and Mr. John Hopkins, F.R.C.S., became members of the Committee, and the investigation was continued. The report of the Committee was published in the *British Medical Journal* of August 13, 1892, p. 369.

Despite the personal opinions of individual members of the Committee, it was determined to investigate the treatment thoroughly, and to report results faithfully. It was demanded that the Matteiists at least tell of what their remedies were composed, but of course this was refused. The treatments were not to be administered by the members of the Committee, who were merely to "see and admit cures in the making," just as if asked to "see and admit the reality of the miracles at Lourdes." The Matteiists were to give the treatments, and this they agreed to do in "bona-fide" cancer cases, provided they were in the "first or second stages."

The terms of the investigation having been settled, the cases were sent in to the Matteiists for acceptance or rejection. Realizing by this time that they were face to face with possible exposure, they began to hedge, and patient after patient of the many sent in was rejected. Finally, however, five women with cancer of the breast were selected and the treatments were begun.

The cases were watched from week to week by a graduate in medicine whom the Committee employed for the purpose, and the members themselves regularly inspected them. Again realizing that the investigation was to be a thorough one, the Matteiists lost courage, and, through their friend and champion, the editor of the *Review of Reviews,* endeavored to end it.

The Editor wrote to the Committee that the cases were proving to be very stubborn ones, and inasmuch as people were anxiously awaiting their report, it was suggested that they see some "cured" cases and make their report from these. Naturally this was refused.

The members of the Committee had agreed among themselves, entirely apart from any agreement with the Matteiists, to give out for publication no authorized statement during the course of the investigation. When, however, after the treatment had continued for a year, and when an obscure medical journal published a statement concerning the prejudiced attitude of the members of the Committee, this was immediately seized upon by the Matteiists as a violation of agreement, and they refused absolutely to continue the treatment under the observation of the Committee or their paid representative. Nothing that their friend, Mr. Stead, could say had any weight with them. They saw in this their last chance to escape being completely found out, and therefore ignominiously abandoned their patients and gave up the test which the overzealous faith of their friends had unwittingly brought upon them. The Committee then rendered its report.

The potions which the Matteiists used and which they called "electricities" were subjected to chemical analysis. They gave no other reaction than that of distilled water!

It is hardly necessary to add that not one of the five cases was in any way benefited by the treatment.

The report ended with the following words: "There is nothing more to be said. The story is as old as the world. The savage trusts to his amulet; the civilized man, both in the upper and lower circles, submits himself with childish, if not childlike, simplicity to the presence of the quack. It is a strange world; but, such as it is, open and honorable medicine has lived and worked in it, and must make the best it can of so wonderfully varied an environment."

It may be stated that the members of the Committee, feeling so strongly that the public was being deceived by the pretentions of Count Mattei and his followers, and that the vaunted "cure" possessed no efficiency whatever, refused to begin the investigation without first emphasizing their opinion to each of the five patients selected, advising them to seek hospital care and proper surgical attention. This they refused to do, so strong was their belief in the new remedy.

The Mattei "Electricities" were still quoted in European wholesale drug lists as late as 1906.

THE CARDIGAN (WALES) "CANCER CURERS"

It might reasonably be inferred that such an investigation as that devoted to the Mattei treatment, which was watched with particular interest by the British medical profession and the public, would have been sufficient to settle the question of the attitude of the profession with reference to "cures" for cancer, and to absolve them, individually and as a body, from further charges of unwillingness to investigate such methods. This was not the case. In about fifteen years history repeated itself, and the British public and medical profession found Mr. Stead once more championing a "cancer cure," the avowed purpose being, of course, the desire to benefit the victims of the disease.[1]

This time he importuned the Cancer Research Committee to investigate the method of the "Cancer Curers" of Cardigan, South Wales. Upon their refusal, and their reminder of the Mattei fiasco, the editor satirically remarked: "Supposing an angel came from Heaven with an infallible specific to heal instantaneously every case of cancer submitted for treatment, the Cancer Research Committee would refuse to recognize the sudden disappearance of cancer from the maladies of mankind unless they were informed of the precise ingredients of the specific."

This arraignment was made apropos of one of the most characteristically "quack" remedies which has ever come prominently before the public notice.

Daniel and John Evans, two farmers near Cardigan, had been "curing cancer" for a number of years, but it was not until 1907 that their fame, having reached the local newspapers, extended throughout Wales, and thence to the country at large.

My attention was first directed to the "Cancer Curers" by an article which appeared in the *Brooklyn Daily Eagle,* July 14, 1907. Shortly thereafter, at my request, Dr. Mary Hess Brown, of New York City, who was visiting London at the time, went to Cardigan to investigate the claims of these men.

It was found that these rough, uneducated men claimed to

[1] *Brit. Med. Jour.*, "Cancer Cures," editorial, March 23, 1907, p. 703.

cure cancer by means of an ointment made entirely from herbs, according to their statement, containing no mineral caustic of any kind. This ointment was applied to the surface of the tumor (they treated only "external" tumors, and by preference only tumors which had not been cut). Tumors which had been operated upon they likened to a tree cut away from its roots, and such a tumor was unsuccessfully treated by them because they had nothing into which to draw the "roots." They claimed to shrink the "roots" of the growth up into the main tumor-mass, which, when this has taken place, falls off, "like a ripe apple from a tree."

The ointment, or oil, which forms the main part of the treatment, was zealously guarded from the view of even the patients, being kept in a bottle covered with black cloth. Daily applications were made over the affected part, each patient being required to bring his or her own brush to the "surgery" for the purpose. After the application of the ointment the brush was carefully squeezed, the excess being put back into the bottle, and the brush washed and dried before the patient was allowed to go. From these precautions it will easily be seen that it was not a simple matter for members of the medical profession to obtain a specimen of the ointment for analysis. It was thought by some, however, to be a spurge (presumably *Euphorbia resinifera*), a caustic plant; others were of the opinion that it was a chlorid of zinc in different solutions.

Following the application of the ointment the patient was instructed to apply water in which marshmallow leaves had been boiled. Sometimes they were instructed to keep the part covered with a cabbage leaf.

This treatment was continued for weeks and months, and doubtless in many instances was repeated upon more than one occasion during the life of the patient.

In the *British Medical Journal* of December 5, 1908, J. Lynn Thomas, C.B., F.R.C.S., Surgeon to the Cardiff Infirmary, reported a case of cancer of the breast "cured" by the Cardigan "Cancer Curers," with plates illustrating how successfully this "cure" was effected. This patient had received daily treatments for eight months, at the end of which time the cancer was steadily growing. "Eight months," said Mr. Thomas, "of daily applications of 'oil' to the whole skin of a woman's breast, with cancer steadily growing and creeping beneath the skin, is a picture for the public to ponder, and for the public press which encouraged scores of cancer victims to migrate to Cardigan, seriously to consider." "The 'cure,' " he concludes, "is worse than a farce, and one may ask how is suffering humanity to be saved from the tragedy of self-destruction by faith in these direful 'Miracles.' "

The British Medical Association investigated this "cure," and in the book entitled "Secret Remedies. What they Cost and What they Contain," published in 1909, are given the results of their examination. One of the so-called cancers which, like the ripe apple, had fallen from the tree, and had been placed in a bottle and given to the patient, was examined microscopically. This was found to consist of "crusts formed of sloughing parts of the skin and inflammatory exudation, the whole being such a mass as might be produced by the use of an escharotic." When these crusts were subjected to chemical analysis they were found to contain zinc chlorid in considerable amount, together with a very appreciable quantity of an insoluble compound of lead. The healing pill to which reference had been made was also analyzed, and was found to contain 27 per cent. of oil of turpentine, the remainder consisting principally of an ordinary saponifiable oil, probably, according to the report, cotton-seed or olive oil. In addition there was a considerable amount of deposit which proved to be composed almost wholly of barium sulphate, a very insoluble salt, known to water-color painters as "permanent white." It was with characteristic disregard for the truth, then, that the statement was made that the treatment involved the use of no mineral caustic.

Such was the "cure" which called forth the above-quoted satirical accusation against the medical profession.

THE "AESIAB CANCER CURE"

One of the most unique investigations of a so-called cancer cure is that embodied in the "Cape of Good Hope Report of the Select Committee on Mrs. van Niekerk's Petition," published at Cape Town, South Africa, in 1906.

This committee was appointed by Orders of the House of Assembly, on petitions presented on behalf of Mrs. Niekerk, with power to take and call for papers. It consisted of seven laymen and four physicians. Seven days were consumed in taking the evidence, and two days more in deliberation and in the formulation of the report. The report, as printed, embodies the verbatim testimony of all the witnesses, with an appendix which gives the various petitions upon which the investigation was based. An abstract of the report is here given.

The various petitions prayed that Mrs. van Niekerk be authorized to treat cases of cancer and other sores by means of her three preparations, the "Aesiab Cancer Cure," a "healing ointment," and a "blood purifying" mixture. The most important of these was the first, which consisted of about 45 per cent. tartar emetic, 5 per cent. chalk, and 50 per cent. lard. Mrs. van Niekerk had received no medical education; she had no scientific knowledge of cancer or of the action of tartar emetic, nor did she claim to be able to discriminate in all cases between cancer and syphilis.

At the suggestion of the committee, Mrs. van Niekerk submitted three patients who had been treated and "cured" of cancer by her method. One of these came by invitation from the committee. The only case from which they could obtain any indisputable evidence concerning the nature of the "cancer" was that of the woman who had used the ointment for two years and four months to remove an alleged cancer of the breast. In consequence of the treatment about three-quarters of the breast had been removed in pieces about the size of walnuts. These pieces the patient had preserved, and they were subjected to microscopical study by the Medical Officer of Health for the Colony. Despite a very careful examination, this official was unable to find any trace of cancer.

While there was no evidence of a cure in any authenticated case of cancer, the details of two deaths had been submitted to the committee. In both cases the treatment had caused needless pain and suffering and appeared, not only to have hastened the death, but to have made it horrible.

The various petitioners had emphasized the philanthropic side of Mrs. van Niekerk's treatment. The committee found, on the contrary, that she had charged an exorbitant price for the ingredients, and had made claims which raised false hopes and caused deplorable loss of time.

The committee denied the prayers of the various petitioners, and in conclusion regretted that the sale of such remedies should be tolerated.

DAVIS CANCER "CURE" (MELBOURNE, AUSTRALIA)

Another interesting example of legislative investigation of an alleged cure of cancer is found in the Davis Cancer Cure, Melbourne, Australia.[1]

[1] "CURE OF CANCER.—Report of Board Appointed to Inquire into the Claims Made by Mr. J. A. Davis in Respect of His Alleged Remedy for Cancer. Presented to Both Houses of Parliament by His Excellency's Command." Victoria, 1911.

The Board was appointed and was constituted by an Order in Council in December, 1906, "to inquire on oath, investigate, and report as to the efficacy or otherwise" of the alleged cure. The Board consisted of ten members, four of whom were physicians. An officer of the Health Department was Secretary. It opened its meetings in January, 1907, and held fourteen meetings between that time and March, 1908, when it adjourned, in order to allow Mr. Davis, the "cancer curer," to complete the treatment of a number of cases under observation. A Progress Report was rendered at that time. The Board resumed its sessions in May, 1909, and held one meeting.

"After having ascertained that none of the cases which were under treatment when the Board adjourned in 1908, and which were as far as practicable kept under observation for more than twelve months, could be produced as cases of successful treatment, the Board decided, in view of the unsatisfactory attitude of Mr. Davis throughout the investigation, to bring the inquiry to a close."

The claims made by Mr. Davis on behalf of his treatment were as follows:

"1. That the alleged remedy, a local application, is effectual in the treatment of cancer, and that, by destroying and causing the removal of the cancerous growth, it cures the disease, leaving no tendency to recurrence.

"2. That the remedy in destroying cancerous growths exercises a selective action and does not affect healthy tissues.

"3. That the remedy is unique and is not in any way identical with other destructive agents (caustics or escharotics) which have in the past been used for the removal of cancerous and other growths, and that it is used solely by him."

According to the report, Mr. Davis, at the beginning of the inquiry, furnished a list of persons whom he desired to call as witnesses. Many of these, he stated, had been treated for and cured of cancer; others were patients still under treatment. He also named a number of medical men who had previously treated patients included in the list.

"The Board resolved to examine those persons who were said to be still under treatment, and in the first instance to make inquiries by letter from those stated to have been cured. Those patients were requested to furnish the names of medical men who had attended them, and full information was afterward sought from each of the practitioners named. It was further decided that any case in regard to which the information thus elicited gave any indication of the disease having been cancer should subsequently be examined.

"Mr. Davis was also specially invited at the outset of the inquiry to submit for examination and investigation all cases which from that time presented themselves for treatment by him, and were, in his opinion, cases of cancer. It was arranged that all the medical members, or as many as were available at any time, should examine such cases at any convenient time, if brought or sent by Mr. Davis to the Chairman before the commencement of treatment. The purpose of this arrangement was to allow of a diagnosis being made before the growth or diseased part had been altered by treatment, seeing that caustic agents may so modify the tissues attacked by them as to render them unrecognizable. It was pointed out to Mr. Davis that the cases which the Board could have under observation and within its knowledge from the inception until the termination of treatment would afford the best and most unequivocal evidence of the efficacy or otherwise of the agents employed by him. It was also explained that cases examined after treatment had commenced, or after alleged cure, would, unless the Board could examine the growth removed, and could identify it with the case, necessarily carry less weight; and, further, that old cases presented long after alleged cure would for the purpose of the inquiry be of small value unless the history and the collateral evidence as to the nature of the growth were unequivocal and positive.

"Mr. Davis agreed to comply with the Board's request regarding new patients, but, although repeatedly invited and urged to carry out the arrangements made, he failed almost entirely to do so, and brought forward, with only four exceptions—

(a) Cases of which the treatment had terminated.

(b) Cases under treatment prior to the opening of the inquiry.

(c) Cases of which the treatment had been commenced after the inquiry had opened, but which were not submitted for preliminary examination as had been arranged.

"Mr. Davis also wished to submit for investigation cases which he admitted were not cancer, but the Board could not see its way to agree to this course, in view of the specific terms of its appointment and of the inevitable clouding of issues which would have resulted from the adoption of such a course."

For the purpose of the investigation, it was considered necessary for the Board to form a conception of the essential nature of those morbid growths which are classed as cancerous. This having been done, the Board proceeded to examine 46 witnesses, of whom 32 had been or then were patients of Mr.

Davis. Eleven witnesses were medical practitioners, who were examined with regard to fifteen of the patients whom they had formerly seen or treated, or with whom they had been otherwise professionally connected.

As a result of its inquiries and investigations, the Board rendered the following conclusions:

"1. That nothing which has transpired since the issue of Progress Report calls for the cancellation of any of the findings set out in that Report (see Appendix "A" to this Report).

"2. That none of the claims made to the Board by Mr. Davis has any foundation in fact.

"3. That the statement that the substance is unique or essentially different from old and largely discarded caustic agents is incorrect.

"4. That the substance used by Mr. Davis is essentially an arsenical preparation.

"5. That arsenic is a well and long-known escharotic or destructive agent, destroying any live tissue with which it is brought into intimate contact. It does not exercise any marked selective action, that is, it does not destroy cancerous tissue and leave healthy tissue unaffected.

"6. That the substance used by Mr. Davis is not an effective means for the treatment of cancer. When applied for a sufficient length of time to any portion of the surface of the body, it acts as a caustic or escharotic, and destroys tissues, whether healthy or diseased, with which it is in contact. In this way a small superficial growth might be removed by the application of the substance, but no action is exercised upon the more deeply-seated cancerous deposits which may be present, even in the case of small and apparently superficial growths.

"The simultaneous complete eradication, not only of the primary superficial growth, but of the secondary deeper deposits, is the essential feature of the effective treatment of cancer.

"7. That the evidence clearly revealed that Mr. Davis is ignorant of the essential nature and evolution of the disease which he claims to be able to cure, and of the mode of its extension and the consequent indications for treatment.

"As a result of this lack of knowledge, wholly unnecessary suffering must have resulted from the use of the treatment after the disease had established itself in other parts than that first attacked. The Board saw cases, and had before it evidence of other cases, in which this had occurred.

"8. That no case unequivocally diagnosed (by microscopical examination) as cancer by the medical members of the Board was subsequently produced cured, or with the growth removed.

"The Board is of the opinion that public safety demands a certain degree of public control of the medical treatment by irregular practitioners of cancerous (malignant) growths and allied diseases, and that persons suffering from such diseases should be protected in some measure from exploitation by irregular practitioners.

"It is therefore recommended that any such practitioners claiming to treat cancer and allied diseases should be required—

"1. To notify to the Department of Public Health his name and address (also any change of address).

"2. To lodge with the Department a copy (duly sworn to) of the formula of any preparation used in the treatment, together with certified specimens of the preparation and a description of the method of treatment.

"3. To report each case which he undertakes to treat so that an investigation could, if deemed advisable, be carried out by competent officers commissioned by the Department.

"4. To forward to the Department copies of any advertisements issued in respect of such treatment.

"If these recommendations are adopted, it is considered that in the necessary legislation provisions should be made

"1. For the prohibition of objectionable or misleading advertisements by such practitioners.

"2. For the restriction of practice in any case after due inquiry.

"3. For the advertising of the facts in any case of restriction of practice."

The evidence, taken in shorthand, is published in appendices to the report.

The total cost of investigation was 123 pounds 16 s. 5 d.

It is a pity that other countries do not follow these examples of legislative investigation of an alleged cure for cancer which is in opposition to the known facts of medical science, and thus deprive the whole criminal brood of "cancer quacks" of the liberty of treating this disease by means of secret remedies. Such investigation, confined within the ranks of the medical profession, may easily be advertised as "persecution" by the particular quacks involved, and thus, instead of ending, may augment the evil. A committee of intelligent laymen working with physicians in the taking of evidence concerning such "cures," many dozens of which are daily being advertised in the public press in this country alone, would accomplish much toward their complete elimination.

There should be some central clearing-house (such as is furnished by the Imperial Cancer Research Fund) for information concerning all such methods and measures; the duty of such an institution or body being to enlighten the public, upon request, or by a systematic campaign of education concerning the criminal frauds being perpetrated against this most unfortunate class of sufferers. In another chapter the subject of educating the public with reference to cancer is discussed more fully.

SUMMARY

The foregoing review of some typical instances of the more or less formal investigation of cancer "cures" emphasizes the possibility for harm which comes with the premature exploitation, in the medical or the secular press, of any method of treatment. It cannot be unqualifiedly asserted that one or a hundred cases successfully treated by a given method establishes its value with sufficient positiveness to warrant the application of such a method to the exclusion of surgical intervention. A test with negative findings, on the other hand, if fairly conducted in a reasonably large number of cases, may be said to afford ample justification for the abandonment of such a procedure.

The study of the many agents and methods which have been employed in the treatment of cancer leads to a reiteration of the statement that, in the present state of knowledge, surgery offers the only dependable hope of cure. Other measures may be employed, but only as adjuvant agents.

SECTION X

NON-SURGICAL TREATMENT

CHAPTER I

CAUSTICS OR ESCHAROTICS

It has ever been a characteristic of human psychology to attempt to utilize the "elements" in the treatment of human ailments. Until quite recently, when the imitation or reënforcement of the natural processes of healing became possible, as seen, for example, in the case of diphtheria, this has been the natural course of events after every advance in physical or chemical knowledge. The direct application of fire, in ancient times in the treatment of the ailments of man, is doubtless the origin of the present-day custom of treating horses by "firing." The most modern illustration of this resort to the elements is the application of radium to cancer; for, however rational the use of this power may become, in its beginning it was little more than primitive empiricism.

The destruction of a tumor *in situ* has always been the alternative to cutting it out, and in all probability it is the older of the two proceedings. The means of destruction that have found favor from one age to another have varied with the knowledge of the times. The red-hot iron was no doubt the successor of the red-hot stone, and each was possibly used with the idea that, while sparing other parts, it would exercise a specific action upon the part to which it was applied. The wished-for localized action, in all probability, was attained in so far as immediate results were concerned; and in early times, when the patient died—for reasons which we may suppose were various—death was probably dissociated from the crude attempts at treatment.

The mysticism of the alchemists was associated, not only with the search for the philosopher's stone, which was to turn base metals into gold, but also with the pursuit of the "elixir of life" and a "cure all" for disease. The alchemist found his medical successor in the apothecary, with his vested right not only in the compounding of medicines, but, in England, even in the power to grant the privilege to practice medicine. Among the general run of people this traditional authority of the apothecary is kept alive by the readiness with which a druggist is often consulted, rather than a member of the medical profession, whenever the patient has a pang of conscience aroused by the symptoms of illness.

In other respects the world is not yet entirely free from the traditions of old. Reputable members of the clergy may be found who still maintain, with as much vehemence as in the days when monasteries abounded and each had its garden of healing herbs, the traditional claims of the church to healing powers. "Old wives' remedies," as they are called, still have their vogue, and the herbalist still thrives on credulity and ignorance.

In no disease is this more true than in cancer, for, in addition to "old wives' remedies" and "herbal cures," actual destruction of tissues by heat (for example, hot air under pressure), and by other ancient caustics, such as arsenic, chlorid of zinc, sulphuric and nitric acids, still find advocates.

In earlier times, it must be admitted, there was sound excuse for seeking an alternative to the knife, whose use was frequently followed by pyemia, erysipelas, and excessive or uncontrollable loss of blood. Applied to an ulcerating cancer, arsenical, mercurial, or other caustic paste did not cause pyemia —it was an unintentional antiseptic application—and therefore often entailed less *immediate* risk than the use of the knife. When death ensued after some temporary relief, if it were not due to the advance of the disease, or to the sudden erosion, by the caustic, of a blood vessel, knowledge was not sufficiently advanced at first to lay the blame on arsenical, mercurial, or other poisoning, which later came to be recognized as its cause. When applied to tumors covered by sound skin, such caustic pastes were found to be without effect. Therefore the skin was destroyed by vitriol or cut into, and daily cuts were made deeper and ever deeper into the tumor to facilitate penetration by the caustic. Results were then obtained like those for ulcerating tumors.

In this way, fostered by the hope which was father to the thought, the theory was possibly built up that caustics exercise a selective action upon the cancer cells while sparing healthy tissue. This theory was long acted upon, in all good faith, and is advocated to-day by ethical physicians who put forth fresh claims to cure cancer by caustics which are asserted to have a specific action on cancer cells.

When once the old mineral caustics, such as arsenic, tartar emetic, and chlorid of zinc, were found not to have a specific action and to be dangerous to health when absorbed, it was but natural that others of less easily definable constitution, and supposed to be less harmful, should be employed. Thus it came about that sulphuric and nitric acids were introduced, with the necessary additional precautions, as were likewise acetic and chromic acids.

Many escharotic vegetable juices, such as that of euphorbia, also acquired prominence. Among more recent examples may be mentioned jequirity, which is an active vegetable irritant and protoplasmic poison. The older traditions are maintained by formic acid, formalin, and potassium bichromate, all three of which are interesting, if only for the reason that they are used by histologists to harden normal and pathological tissues, including cancer, for the purpose of preparing them for microscopical study. Inserted into the body, their immediate or direct action is not restricted to the tumor tissue, but extends to all the tissues with which they come in contact. They may have remote effects on other organs like those which result in chronic arsenical or mercurial poisoning, particularly if they lead to blood destruction or to damage to the kidneys. They are dangerous drugs, not prescribed in any circumstance whatsoever in doses exercising so much of their poisonous effects as would be produced by absorption when employed in the way they are recommended for cancer.

The employment of caustics has become ever and ever more limited. There was a time when, although they were no longer advocated as cures, they were still applied during the waiting stage, during the "precancerous" period, when an ulcer, for example, of the tongue, was being watched to see if cancer would develop. The disastrous consequences of this "waiting" have been well emphasized by Butlin. (See Section V, p. 133.) To-day the practice is abandoned, except among a few who use mild caustics like alum or silver nitrate upon ulcers in the early stage of the precancerous period. This only serves to invite, by irritation, a malignant process. Thus a modern physician or surgeon is not an unbiased critic of the method, which may be more fittingly set forth in the words of one who gave it an impartial trial in the days when it was still in vogue, before surgery had attained to anything like its present development. This purpose is fulfilled by the description of C. H. Moore, of the Middlesex Hospital, London.

In 1870, in the second edition of Holmes' System of Surgery,[1] Moore was associated with Sir James Paget in the articles on cancer. Regarding treatment by caustics, Moore wrote:

"By means of caustics efficiently used, it is possible to destroy the vitality of a whole tumour and obtain its complete removal; but the pain ordinarily occasioned by them forbids their employment when chloroform and the knife are not contra-indicated. Caustics exert no especially curative action upon cancer structures, but they present two advantages over a cutting operation. Their employment is not attended by an effusion of blood and the consequent exhaustion, or by erysipelas or pyemia. And, further, in most cases they occasion a considerable emaciation of the healthy tissues adjoining the slough, and a diminution in the size of glands secondarily affected with cancer. Among many patients treated in the Middlesex Hospital with caustics in the summer of 1857, there was a marked difference in the effects. In some it appeared to act in the same manner as erysipelas and hospital gangrene. Apparently, but in fact incompletely, removed, the disease reappeared in a few weeks; in those cases, however, in which caustics were carried through the cancer into healthy tissues no such recurrence took place before the healing of the wound. After that event, the cases treated by caustics followed the ordinary course of cancer. Disease reappeared, and death ensued as usual.

"None of these results of the use of caustics differ materially from those which attended a cutting operation, and in cases which are equally adapted for either, British surgeons do not resort to caustics. There are some instances of advanced and ulcerated cancer, however, attended with suffering, but having adhesions which could not be detached with the knife; and in these a gradual insertion of caustic is sometimes followed by the complete enucleation of the tumour and cicatrisation of the wound. In a case of medullary cancer of the parotid region, of very rapid growth, and so full of blood vessels as to pulsate and bleed severely, the writer first tied the carotid artery, and then employed the caustic paste. The comfort and prolongation of life resulting from such treatment reconcile the patient to the temporary pain by which those advantages are gained.

"If, on such grounds as the less probability of a fatal result from the mode of proceeding, it be determined to treat a pri-

[1] Moore, C. H., in "A System of Surgery, Theoretical and Practical, in Treatises by Various Authors," edited by T. Holmes. 2nd ed. Vol. I, General Pathology. London, 1870, p. 605.

mary cancer with caustics, the general rules must be observed which are applicable to the selection of cases for a cutting operation. The tumour must be primary, solitary, and uncomplicated with evident constitutional disease or infection of the parts around it. Should the absorbent glands be affected, the operation by the knife is decidedly preferable to that by caustics, as it is difficult to remove glands by the latter method.

"There are various methods of cauterizing a cancerous tumour. If a liquid be chosen, its application must be limited by some contrivance; as, for example, a hoop or cylindrical tube of gutta-percha, set on its edge around the tumour, and closely glued to the skin by means of a solution of the same material in chloroform. The caustic liquid, poured into the cup thus formed, or laid in it as a paste made with saffron or sawdust, will then burn through the diseased mass, the depth of its action being determined beforehand by the quantity of the caustic employed. The strong sulphuric acid and the fuming nitric acid produce a dry, hard, and much-concentrated eschar, which separates spontaneously in the course of from one to four weeks, and leaves a granulating and cicatrising sore.

"Chloride of zinc may be made into a cake or a paste with flour, or may be employed alone. It can only be used upon a denuded surface. If the skin is entire, it must be first blistered or killed with the concentrated nitric or sulphuric acid. The chloride may then be laid over the tumour and allowed to penetrate through it. When the cancer is already ulcerated, the zinc-paste, diluted for the first application, may be soaked through cotton-wool and introduced into the ulcer. The caustic, infiltrating the tissues, coagulates their albumen and blood, and produces a slough, which is friable, inodorous, and less dry than that resulting from the acids, but which separates in the same manner.

"When white arsenic was employed, it was mixed with calomel, or bichloride of mercury, or merely with flour, and laid in very small quantity upon a raw surface over the cancer. Like the chloride of zinc, it is inert if applied to the skin. A very small quantity, not more than two or three grains of this caustic, was used at a time; but as it became absorbed, and some patients died in consequence, the use of it has been abandoned.

"A convenient plan for extirpating a cancerous tumour, and one which keeps the action of the caustic within the control of the surgeon, is to lay the paste of the chloride of zinc within a cancerous ulcer, or on skin previously destroyed by a strong acid, in the manner already described, and, through incisions deepened daily as the slough extends, to introduce fresh quantities of the same caustic, until the whole tumour is perforated and destroyed. It is then cast off, and a healing wound occupies its place. The process is a slow one, and portions of the tumour are apt to be left behind and to require a renewal of the treatment. It is also sometimes incapable of overtaking the progress of a very rapidly growing cancer. But it is ordinarily less painful than any other cauterization, and is applicable in some cases in which a tumour is so situated that the knife could not be used. Thus the effective part of the treatment introduced into England by Dr. Fell, of the United States, was described at length, and an estimate of its surgical value offered, in a *Report on the Treatment of Cancer in the Middlesex Hospital in 1857.* In making the paste it is desirable to use a saturated solution of the chloride of zinc.

"Mr. Shaw has favoured me with the following interesting memorandum:

" 'Mr. Whitbread introduced to Sir C. Bell a Dr. Chuna, son of a physician at Lisbon, and who treated cancer of the face with a powder called by his name. It was made up of one part of tartar emetic and two of sulphate of zinc. It was used by scarifying along the outer edge of the ulcer, and filling the cut with the powder. It raised a great inflammation, on the subsidence of which the spreading ceased. I remember Sir C. Bell employing it in a rather elderly male hospital patient. The only effect I can recall is that great tumefaction and exceedingly severe pain followed, and that the results deterred Sir Charles from using it in any other case.'

"The hypodermic injection apparatus has been used by Sir J. Y. Simpson for the purpose of injecting into tumours caustics in a liquid form, and by means of it he succeeded in destroying a fatty tumour. The same apparatus, employed independently by Dr. Broadbent, furnished the means of introducing solvents into the substance of cancers, and he has actually succeeded in dissolving away tumours of that nature in the living body. He selected the acetic acid for its known chemical effects on cancers under the microscope, and diluted it with three times its bulk of water. The injection of a few minims or a drachm into a cancerous tumour is immediately painful, but if any escape into the adjoining textures, the smarting is severe. After a temporary redness and swelling, the tumour is found smaller, and it may eventually disappear. By a single injection Mr. De Morgan and I have each succeeded in obtaining such gradual diminution of cancerous tumours, which have not reappeared for two years and a half. That this remedy acts as a chemical solvent of the cell was shown by a specimen which I exhibited at the Pathclogical Society of London. (Transactions, Vol. XVIII, p. 236.)"

Since Moore's observations were published, 44 years have elapsed. Experience with the caustic treatment of cancer, accumulated in the interval, more than justifies his judicious reluctance to resort to the method, more especially in the light of the advances of surgical technic which he advocated but did not live to see carried out. The caustics he mentioned are even now occasionally heard of in ethical practice; they are still the common stock of the quack.

In professional practice arsenic has changed its form into atoxyl and salvarsan; acetic acid appears in the form of its near chemical relatives, formic acid and formalin, and chromic acid is now known as potassium bichromate. On more rational grounds we have newer destructives of rapidly growing tissue in X-rays, radium, and mesothorium. These will be considered separately *Vide infra,* Chapter II), not only for the reason that they maintain the continuity of mankind's search for a rational substitute for the knife as a cure for cancer, but also because at present their use appears more rational than the indiscriminately destructive caustics of old.

The list of "useful" caustics has been reduced by some advocates of this method to five, viz.: potassa fusa (caustic potash); zinc chlorid; strong sulphuric acid; iron chlorid; arsenic. Of these, zinc chlorid and arsenic, in various pastes and other combinations, have been most extensively used.

Zinc chlorid, in one form or another, has been more widely employed perhaps than any other caustic agent. With the addition of this or that agent, it has been exploited as a "new cure" from time to time for many years.

Probably one of the most conspicuous examples was the "Dr. Fell Treatment," tested by the Middlesex Hospital in 1857, already mentioned. In this instance zinc chlorid was mixed into a glutinous paste, which, in advanced cases, was applied directly to ulcerated surfaces, or, in cases in which the skin over the tumor remained unbroken, to the tissues exposed by means of "progressive incisions."

Canquoin's paste, consisting of zinc chlorid and flour, is one of the most widely used forms of this escharotic agent.

Bougard's paste has for one of its chief ingredients zinc chlorid.

Zinc chlorid solution, 30 to 50 per cent., was more extensively used by the late J. Marion Sims than any other form of treatment. He applied it, on pledgets of absorbent cotton, in the hole made by the curet.

Zinc chlorid solution, 5 per cent., has been used for parenchymatous injection.

It has been maintained by some writers that zinc chlorid destroys only cancerous structures; others who have carefully experimented with the agent do not accept this view.

Arsenic and its derivatives, as remedies in the treatment of various diseases of the skin, received mention from the earlier medical writers. Fuchs, in 1594, employed it externally in the treatment of cancer. It was not, however, until the early part of the nineteenth century that it became a recognized agent in the treatment of malignant diseases. Its use, in various forms—powder, paste, solution, etc.—was extended after this, until it finally came to play a conspicuous part in the treatment of cancer. It forms the chief ingredient of many of the pastes and plasters employed at the present time by some of the ethical as well as the unethical members of the medical profession.

Interest in arsenic, in the treatment of malignant disease, was given an impetus in 1897, when Cerny and Trunecek reported their experience with a *hydro-alcoholic solution of arsenic* acid.[1] The method found many adherents for a time, and is still used to some extent.

Manec's paste consists of arsenic, cinnabar, and burnt spurge.

Marsden's paste contains arsenious acid and powdered acacia.

Bougard's paste, previously mentioned, contains arsenic.

Parenchymatous injections of arsenious acid have been tried by a number of investigators. A few have recorded favorable results, while others have reported the contrary.

"Arphoaline," a combination of arsenic with phosphorus in albumin, employed internally and by local application, has received a limited degree of attention.

In addition to zinc chlorid, and arsenic and its derivatives, many other agents have been employed for their caustic properties. Among these may be mentioned: acetic acid (injected into growth); bromin (painted around cancer); carbolic acid (injection)—dangerous; chromic acid (potassium bichromate); formic acid (formalin)—probably dangerous; nitric acid; papain as injection; pepsin; perchlorid of iron; potassa fusa (caustic potash); sulphuric acid (with half of lime—

[1] Cerny and Trunecek.—"Guérison radicale du cancer épitheliale," *Sémaine médicale,* May, 1897, XVII, p. 161. See also: Vignat, Marcel.—"Contribution à l'étude de la Méthode de Cerny et Trunecek," *Thèse de Paris,* 1900.

Vienna paste); tartar emetic; terchlorid of antimony; zinc sulphate; chlorid of gold; thoremiden, or thorium paste (Semerak). Many others, particularly mild caustics of vegetable origin, have been utilized. In many of the so-called cancer cures the juices of the various plants of the *Euphorbia* family, and also jequirity, have been used, generally in connection with other substances.

The advocacy of caustics by ethical practitioners of the present day is presumably based, as Park [1] has pointed out, upon the assumption that the resulting reaction tends to block lymph channels, and, in consequence of the violent and extensive reaction, to produce "a sanitary cordon of fresh inflammatory tissue which walls off the area of pathologic activity and may also destroy scattered cancer cells." Still it is doubted if any such effective cordon is produced, because the caustic action is not limited to the cancer.

In epithelioma of the skin, aside from cases which demand extirpation of contiguous lymph glands at the time of removal of the growth, excision, according to Pusey,[2] is not as good a method as the application of X-rays or caustics. The objection to excision, he says, is "that the outlying radicals of the tumor extend well beyond the apparent border of the growth, and their removal by excision requires the sacrifice of a great amount of healthy tissue. The deformity which results is therefore great. But a more important objection is that even the most careful surgeon is apt to fail to get all traces of the growth, so that recurrence is common."

Few surgeons would accept these objections. The selective action of caustics has not been sufficiently well demonstrated to warrant the belief of some dermatologists that any such agent is to be relied upon to search for and destroy outlying radicals which cannot be found by the surgeon. It is safe to say that, if these radicals extend far enough beyond the "apparent border" of the growth to require the sacrifice of a great amount of "healthy tissue" in order to remove them by excision, the supposedly healthy tissue is doubtfully so, and should be removed to insure against recurrence. The objection with reference to deformity is usually easily overcome by skin grafting or plastic surgery. The last objection, with reference to failure to get all traces of the growth, involves, again, the

[1] Park, Roswell R.—"Recent Views Concerning the Treatment of Cancer, Based upon Its Nature," *Buffalo Med. Jour.*, April, 1911, p. 465.

[2] Pusey, William Allen.—"The Principles and Practice of Dermatology," 1911, pp. 912-13.

selective action of the caustic agent, which is always a debatable factor.

The difference of opinion among dermatologists and surgeons is accounted for by Stelwagon [1] by the fact that the cases coming under the observation of the dermatologist are relatively superficial and slight, circumscribed and slow, whereas those coming under the care of the surgeon are of more serious nature. Certainly the former class includes the only cases, to my mind, in which there is any excuse for the use of caustics, with the exception, of course, of cases in which surgical removal is absolutely refused.

The cases usually seen by the dermatologist, and often reported as successfully treated by curet or caustic, are of squamous cell epithelioma, relatively non-malignant, and are not to be considered when describing real malignancy—true cancer.

Of the large number of chemical agents which have been applied to cancer, it is safe to state that in the majority, if not in all instances, whatever beneficial effect is exerted is due to the caustic action of the agent itself or of some ingredient employed in its preparation for use in the treatment of cancer.

A number of agents, notably cholin, colloidal copper, and selenium, have recently been proposed for the treatment of cancer, alone or in conjunction with X-rays or radioactive substances, but no convincing reports of their curative efficacy have yet appeared. For this reason space need not be used for the details concerning them.

SUMMARY

The extensive studies that have been made to determine the factors which predispose to the development of cancer have given a place of great importance to irritation. The therapeutic outcome of such conclusions is that treatment should be sedative rather than irritative. Sedation, and not irritation, is the watchword wherever cancer has been, or is likely to be, present.

This being true, caustics have practically no place in the treatment of malignant disease where there is hope of cure; certainly not in other cases than those which are known to be superficial, slight, circumscribed, and of slow growth. Even the most expert diagnostician, however, may be unable, at times, to make this differentiation. Furthermore, it is to be remembered that a growth may be small, apparently slight and circumscribed, and yet be very virulent in that it possesses great power for the formation of metastasis. Unless a caustic destroys every vestige of malignancy, in such a case, before metastasis has occurred, its use merely augments the danger.

[1] Stelwagon, Henry W.—"Diseases of the Skin," 1914, p. 885.

CHAPTER II

PHYSIOTHERAPY

HEAT, LIGHT, ELECTRICITY, RADIO-ACTIVITY

In 1792 George Adams, Mathematical Instrument Maker to His Majesty, and Optician to His Royal Highness the Prince of Wales, reproached the medical profession for lack of tenacity of purpose in its use of electricity, at the same time forecasting the history of electrotherapy as applied to cancer at the present time. In his book on electricity[1] he says: "The science of medicine and its practitioners have been reproached with the instability and fluctuations of practice; at one time cold as the ice at Zembla, at another hot as the Torrid Zone; that they are led by fashion and influenced by prejudice. On this ground it has been predicted that, however great the benefits which may be derived from electricity, it would still only last for the day of fashion, and then be consigned to oblivion."

Adams declared that electricity had "considerable scope for action" in surgery; tumors, particularly of the glandular sort, being included in the catalogue of "visible diseases as distressing to the sight of others as to the patients themselves," which might be benefited by this agent.

On glancing over the voluminous but inconclusive literature of the electrotherapeutic treatment of cancer, the prophetic insight of this early observer is borne out nearly two hundred years later. What applies to electrotherapy is equally true of its concomitants, phototherapy and radiotherapy.

HEAT

Heat, *per se,* seems to have received little attention. Its therapeutic value in the treatment of cancer has not been en-

[1] Adams, George.—"An Essay on Electricity, Explaining the Principles of that Useful Science; and describing the Instruments Contrived either to illustrate the theory, or render the Practice entertaining, etc." 4th edition, 1792, p. 494.

tirely dissociated from the action of light and electricity, except as it has been applied, by one means or another, for the relief of pain and other symptoms, or for a purely cauterant effect. It will therefore not receive separate consideration here. Its presumptive causative rôle in the production of cancer is generally attributed to the factor of chronic irritation, as seen in the natives of Kashmir, who use the Kangri basket (see p. 67).

LIGHT

The therapeutic value of light has been recognized for centuries, yet it is only within recent years that the sunbaths of China, Japan, Africa, and other countries, the "heliosis" of the ancient Greeks and Romans, have undergone a recrudescence and a metamorphosis into modern solartherapy, phototherapy, and actinotherapy, and have come to be applied in the treatment of malignant neoplasms.

SUNLIGHT

The literature which deals with the various methods of treating cancer contains very little definite information concerning the effect of sunlight upon this disease. Widmer [1] reports the cure of a case of carcinoma by repeated exposure to the direct rays of the sun. Bie [2] reported seven out of sixteen cases of epithelioma cured by "concentrated light." The diagnosis in each of Bie's cases was verified by microscopic sections, and the patients remained free from the disease for from six months to two and a half years. Thayer [3] was led by accident to the use of the sun's rays in the treatment of cancer and other affections of the skin, employing first a small lens (sun-glass), then larger and more perfect lenses. During a practice of more than forty years he claimed to have used no remedy which compared with solar heat in its curative power. In the treatment of malignant diseases, he said, the tissues must be fully destroyed or carbonized.

[1] Widmer, C.—"Heilung eines Karzinoms durch Sonnenlicht nebst einigen Beiträgen zur unmittelbaren Lichttherapie," *Münch. med. Woch.*, 1907, liv, 619.

[2] Bie, V.—"Behandlung von Hautepitheliomen mit concentrirten Licht," *Dermat. Zeitschr.*, Berl., 1900, VII, 630-41.

[3] Thayer, O. V.—"Concentrated Rays of the Sun (Solar Cautery) as a Remedial Agent," *Pacific Med. Jour.*, San Francisco (1893), XXXVI, 412-419. Also *South. Pract.*, Nashville, 1893, XV, 360-367. Also: "The Treatment of Cancer, Lupus, and Other Malignant Growths, with Concentrated Sun's Rays—Solar Cautery," *Pacific Med. Jour.*, 1902, XLV, 193.

This method of treatment, according to Thayer, was attended with little pain and inconvenience, no general or local anesthetic being necessary. Only slight reaction and pain followed the application of the rays. The wounds healed sooner than after X-rays. Not more than twenty or thirty treatments were necessary, and, in the majority of cases, not more than ten.

Exposure to strong sunlight, by promoting circulation through the affected areas, in some cases relieves the pain caused by nerve-pressure. Just what part the heat-waves play, aside from their association with the luminous rays, cannot be stated.

The actinic rays of the sun are thought to play little or no part in whatever action solartherapy, by means of the sun-bath, may have upon cancer; for, as Finsen has shown,[1] the blood acts as a barrier to the passage of these rays through the tissues, necessitating the preliminary more or less complete exsanguination of the part to be treated.

The therapeutic application of concentrated sunlight was formerly made by means of various lenses, "sun-glasses," or "burning glasses." Finsen devised a concentrating apparatus which not only gave a convenient means of applying the rays, but which enabled him to filter out the calorific and luminous rays. The uncertainty of the sunlight led to the almost complete abandonment of this method in favor of artificially produced light.

Seelye[2] has recently reported the successful use of concentrated sunlight in the treatment of superficial epitheliomata and malignant ulcers.

ELECTRICITY

ARC LIGHT

Finsen inaugurated the scientific treatment of disease by the application of light, and his Light Institute, at Copenhagen, has been the Mecca for students of light-therapy. Finding the electric arc light to be richer in ultra-violet rays than sunlight, he devised large arc lamps, the rays being focused by quartz lenses cooled by a stream of water. This original Finsen lamp has undergone various modifications, looking to utility and portability. There are now to be found numerous solar arc

[1] See Bie, V.—"Remarks on Finsen's Phototherapy," *Brit. Med. Jour.*, 1899, Vol. 2, p. 825.

[2] Seelye, Hiram H.—"Cutaneous Epithelioma Cured by Sunlight," *New York Med. Jour.*, February 7, 1914, p. 279.

lights, among which may be mentioned the Finsen, the Finsen-Reyn, the Quartz Mercury Vapor lamp, and the Kromeyer lamp.

The arc light has been successfully employed by Finsen,[1] Petersen,[2] Burgsdorf,[3] and others, in the treatment of epithelioma during the early stages. It has not been used for carcinoma when not situated on the surface of the body, or for sarcoma, and has been practically abandoned even in the cases of superficial epitheliomata.

As a purely palliative measure the arc light in its various forms has been employed by a number of investigators.

The study of the action of light on the lower forms of both vegetable and animal life, in Hyde's[4] opinion, points to the probability that in man exposure to actinic rays produces a perceptible stimulation of the skin; and that this stimulation is effective in proportion to the special irritability of the integument on which it falls.

"It is important," he says, "to recognize the connecting links in this chain of events associated with all radioactive phenomena, for the reason that, in the case of the rays most carefully studied, therapeutical are intimately bound up with pathological results. Thus the action of the Finsen light upon the skin produces a well-known reactive hyperemia, though the technic of its application demands that the area to be treated should be made as exsanguine as possible by pressure in order to permit the passage of ultraviolet rays to the skin. With this end in view an attendant is required to press firmly upon the patch of skin subjected to the ray a cell of quartz crystal through which water continuously flows and which is held in position during the entire séance."

INCANDESCENT LIGHT

Numerous therapeutic incandescent lamps have been placed on the market, a number of which have been made the subjects of extravagant claims with reference to the cure of all manner of diseases, including cancer. These lamps range from fifty

[1] Finsen, Niels R.—"The Treatment of Lupus Vulgaris by Concentrated Chemical Rays": . . 1897. Appendix to "Phototherapy," 1901.

See also: "Mödd. om de hidtil opnaaede Resultatear af Behandlingen af Hudepitheliomer med. konc. Lys," *Dermat. Selskabs Forhandl.*, 1899-1900.

[2] Peterson, O. V.—"Progress of Phototherapy by Finsen's Method," *Vrach*, St. Petersburg, 1901, XXII, 1369.

[3] Burgsdorf, V.—"Curative and Noxious Powers of Light," *Kazan Med. Jour.*, 1902, Vol. II, 517-528.

[4] Hyde, James Nevins.—"On the Influence of Light in the Production of Cancer of the Skin," *Am. Jour. of Med. Sciences*, January, 1906, p. 1.

to seven hundred candle power, and have diverse reflectors and other appurtenances for the supposed augmentation of therapeutic value. The *Leucodescent Lamp* has been employed for this purpose, as have doubtless other incandescent lamps; but I have been unable to find a reliable record of the use of *any form* of incandescent lamp in the treatment of any form of cancer. It may be said, however, that no conclusive trial seems to have been made of any of them. It may not be denied, therefore, that they might prove useful as adjuvant measures for the relief of pain and other symptoms of advanced and irremovable cancer, and for the clearing up of discharges and cachexia.

FLUORESCENT STIMULATION

Von Tappeiner and Jesionek,[1] Tousey,[2] and others, have experimented with fluorescent substances in the treatment of malignant diseases.

Von Tappeiner and Jesionek treated three cases of cutaneous cancer by painting the lesions, at frequent intervals, with a five per cent. aqueous solution of eosin, immediately thereupon exposing the part to the rays of the sun or to the light of an electric lamp. In each case (cancer of the face) the ulcerated surfaces became covered with good granulations, the lesions "evoluting toward a cure." Quinin, esculin, and fluorescin have also been used in connection with X-rays and radium. Quinin, in five-grain doses, and esculin, in one-grain doses, in dilute solutions, have been administered internally, a few hours before treatment with X-rays or radium.

Tousey's experiments led him to conclude [3] that the various fluorescent media which have been given internally in conjunction with the application of X-rays have no beneficial result due to the luminosity excited.

X-RAYS

It is claimed [4] that the X-rays, discovered by Röntgen,[5] in

[1] Von Tappeiner and Jesionek.—"Therapeutische Versuche mit fluoreszierenden Stoffen," *Münch. med. Woch.*, Nov. 24, 1903, p. 2042; abstr. in *Sémaine méd.*, 1903, p. 422; and in *Revue International d'Electrothérapie*, January, 1904, No. 13, p. 212.

[2] Tousey, Sinclair.—"Medical Electricity and Röntgen Rays," 1910.

[3] *Op. cit.*

[4] Johnson and Merrill.—"The X-rays in the Treatment of Carcinoma," *Phila. Med. Jour.*, 1900, Vol. 6, p. 1089.

[5] Röntgen was studying the properties of the cathode rays in a partially exhausted tube—Crookes tube. Crystals of barium platinocyanide in the vicinity of the tube became fluorescent, and, upon investigation Röntgen found that the luminosity was due to an undiscovered ray, which he named the X-ray.

1895, were first employed in the treatment of malignant diseases. The history of the therapeutic use of the rays has since verified the prophecy made by Adams in 1792, quoted at the beginning of this section.

Extravagant claims have been made concerning the curative property of this agent, and it will doubtless continue to have its adherents until we gain more definite knowledge concerning the action of the rays and the nature of cancer.

The causal relation of X-rays to cancer has been made the subject of considerable experimental work. In 1907 Porter and White[1] collected from the literature ten undoubted cases of skin cancer produced by the action of the rays, adding one case from personal experience. Since that time the list has been considerably lengthened, many investigators having fallen victims to malignant disease, presumably in consequence of the action of the rays upon the skin.

Rowntree,[2] accepting the well-established fact that prolonged exposures to X-rays have resulted in the production of a new growth, which seemed identical, by microscopic examination, with squamous-celled carcinoma, proceeded to study the pathological changes set up. His studies consisted of the examination of specimens of five cases of carcinoma arising in X-ray workers, in investigations carried out on patients in cancer wards of the Middlesex Hospital, and in experiments with rats.

Microscopic study of the specimens upon which his report was founded left no difficulty in accepting them as examples of typical squamous-celled carcinoma.

The rats upon which experiments were conducted were placed in small lead cages which completely protected their bodies, while allowing their tails to project from a small hole. Exposure to the direct action of the X-rays involved only the dorsal surface of the tail. When thus exposed for a long time, marked dermatitis followed, the entire circumference of the tail being affected at the tip where movement in all directions was possible. Nearer the base, where only the dorsal surface was exposed, the changes were confined to this surface and were well defined. The ventral surface in the locality was normal. The diseased surface showed disappearance of the surface epithelium, the hair bulbs, and the sebaceous glands, and the formation of granulation tissue. The intermediate zones showed thickening, with slight irregularity of surface

[1] Porter and White.—"Multiple Carcinomata Following Chronic X-ray Dermatitis," *Annals of Surgery*, 1907, Vol. 46, p. 649.

[2] Rowntree, Cecil W.—"Contribution to the Study of X-ray Carcinoma and the Conditions Which Precede Its Onset," Archives of Middlesex Hospital, 1908, Vol. XIII, p. 182, and Vol. XV, 1909, p. 192.

epithelium and hypertrophy of the hair follicles. After exposure sufficient to produce severe dermatitis, the bones showed a considerable degree of alteration, giving a much lighter shadow on the skiagraphic plate than the normal bone.

From his experiments Rowntree concluded as follows:

"1. That the application of X-rays to healthy tissue in moderate doses—what may be regarded as a moderate dose probably varying considerably with the idiosyncrasy of the individual—results in stimulation of normal physiologic processes, i. e., the growth of epithelial and other cell elements, hairs, etc.

"2. That a single large dose may result in an acute change somewhat resembling an ordinary burn or other form of destructive dermatitis.

"3. Administration of doses for a long period ultimately results in complete atrophy of the epithelial elements and degenerative changes in the connective tissues.

"4. That the conditions contained in 1 and 3 ultimately result in a state which disposes to the occurrence of carcinoma. Whether the formation of epithelial new growths is simply due to the chronic irritation abundantly present in these cases, or whether the X-rays by their action exert some special influence, it is at present impossible to say."

Clunet,[1] on the other hand, conducted experiments which led to more positive results. He produced a destructive ulcerative radiodermatitis in white rats. As soon as this ulceration was ready to heal, radiation was again applied. At the end of five months, after several spontaneous tendencies to heal, which were at once interrupted by a new exposure, the X-ray ulcers had become sufficiently established to show no tendency toward repair during nine months, although no longer exposed to the rays. One of the four rats treated in this manner developed, nine months after the last exposure, a tumor upon the X-ray ulceration. This tumor recurred after operative removal, and six weeks later caused the death of the animal. Histological examination showed this tumor to consist entirely of connective tissue elements of very unequal size and variable morphology, representing an unusual type of sarcoma. This was the first instance of the experimental production of cancer by X-rays.

[1] Clunet, J.—"Tumeur développée sur une radiodermite expérimentale," Recherches Expérimentales sur les Tumeurs Malignes, Paris, 1910, Chap. X, p. 297.

See also: Marie, Clunet, and Raulot-Lapointe.—"Contribution à l'étude du développement des tumeurs malignes sur les ulcères de Roentgen," *Bull. de l'Association française pour l'étude du cancer*, 1910, No. 3, p. 404.

Marie, Clunet, and Raulot-Lapointe[1] reported further experimentation, resulting in the production of malignant tumors following X-ray dermatitis in two white rats. In the first case the tumor could not be grafted on other animals, whereas the second, which developed under identical conditions, could be transmitted through other animals.

It has not been determined exactly how X-rays affect cancer cells, whether by a direct action or by an electrolytic process. Schmidt[2] conducted a series of experiments with plants in order to determine the action of X-rays. He soaked a number of beans in water for six hours, treated different beans with different doses of X-rays, then planted them. The beans which were given large doses were more or less completely inhibited in growth, whereas those which received small doses were so stimulated that, compared with the untreated beans and those receiving large doses, the plants were larger and more vigorous, the flowers were larger, and the production of beans better. These findings led him to believe that animal cells might respond in like manner to varying degrees of the rays. He experimented upon a sluggish ulcer on the arm, which verified the findings in the case of the beans. This led naturally to three conclusions:

1. That, in treating indolent ulcers and other conditions in which healing and cell proliferation are sought, very small doses of the X-ray should be given.
2. In malignant growths, when the destruction of tissue is the purpose, large doses should be administered.
3. That small doses, in the case of malignant growths, may stimulate cell proliferation and thereupon lead to renewed activity.

If Schmidt's experiments are to be accepted as leading to correct conclusions, it is easily to be seen that the X-ray, unless used in sufficient dosage, is not only an agent of little value in the treatment of malignant disease, but that it is, or may be, fraught with distinct harm, even to the production of malignant neoplasms.

Coolidge[3] has described a new X-ray tube which marks an advance in X-ray science. The tube is so constructed that the penetration and intensity of the ray are under the complete

[1] Marie, Clunet, and Raulot-Lapointe.—"Nouveau cas de tumeur maligne provoquée par une radiodermite expérimentale chez le rat blanc," *Bull. de l'Assoc. française pour l'étude du cancer*, 1912, No. 6, p. 125.

[2] Schmidt, H. E.—"Experimentelle Untersuchen über die wirkung kleinerer und grosserer Rontgenstrahlen-mengen auf pinge Zellen," *Berl. klin. Woch.*, 1910, Vol. XLVII, p. 972.

[3] Coolidge, W. D.—*Physical Review of the American Physical Society*, December, 1913.

control of the operator at all times. A very high degree of penetration can be obtained—of the greatest advantage in the treatment of deep-seated cancer. The time of application is materially decreased. This tube is still on trial. It may be that the extremely hard rays produced by it may act similarly to the gamma rays of radium.

Kassabian,[1] who fell a victim to X-ray cancer, gave a digest, in 1910, of the work of others in the use of X-rays in the treatment of epithelioma, carcinoma, and sarcoma. He found a great diversity of opinion.

In the treatment of epithelioma, he said: "Some prefer the soft and others the hard tube. Views also vary as to the duration of the séances and their frequency. It is asserted by some that a slight dermatitis is always to be aimed at, in order to obtain the proper action. The great variety of the cases encountered will allow no special technic; the peculiarities of the epitheliomas themselves will frequently dictate the method to be pursued."

Reports of X-ray therapeutists, according to Kassabian, are widely divergent as to the value of X-rays in the treatment of cancer. He expressed the opinion that this is largely due to the use of inefficient apparatus and to errors in diagnosis, benign growths being mistaken for malignant ones. He emphasized, in this connection, the importance of examining microscopically, before, during, and after irradiation, sections or scrapings of the growth.

"Probably we err too much," he said, "on the side of safety; apparently the séances are too brief, we too often fearing the production of a severe type of dermatitis." He advised and always used, short, and frequently repeated, exposures.

MacKee[2] favors single massive doses of X-ray in the treatment of epithelioma, and claims that the repeated small doses may result in the production of a resistance to the beneficial action of the rays.

Coley[3] reported sixty-eight cases of sarcoma treated by X-rays, in six of which there was complete disappearance of the disease. In each of these cases, however, there was recurrence within a few months.

Bythell and Barclay[4] state that "sarcomata respond more readily to X-ray treatment than either carcinomata or epithe-

1 Kassabian, Mihran Krikor.—"Röntgen Rays and Electrotherapeutics, With Chapters on Radium and Phototherapy," 1910.

2 MacKee, George M.—"Epithelioma Treated with the Massive-Dose Method," *Jour. of Cutaneous Diseases*, 1913, Vol. 31, p. 411.

3 Coley, W. B.—"Later Results of the X-ray Treatment of Sarcoma," *Archives of Physiol. Therapy*, 1906, Vol. III, p. 161.

4 Bythell and Barclay, "X-ray Diagnosis and Treatment," 1912.

liomata, but metastatic deposits make their appearance at a very early stage in the malignant types." "In our own practice," they report, "we have had three cases that have been apparently cured—one in a case affecting the palate, and two cases of abdominal sarcoma in children."

Schultz[1] says: "There is hardly any object in treating large sarcomata, and especially so if they reach to the periosteum or if they start from the bones. On the other hand, smaller nodules, up to the size of a nut, whether they are intra- or subcutaneous, are often favorably influenced, likewise also primary or metastatic sarcomatous lymphatic glands provided they do not exceed the size of a hen's egg."

Jones[2] considers that, while there is a quantity of evidence to support the contention that X-rays act beneficially in malignant disease, "the amount of evidence to show that cures have resulted is lamentably meager, and we cannot yet suggest any explanation why an agent which very commonly gives relief to some of the symptoms produced by malignant growth should fail to give the complete relief which is really required, and we are almost forced to believe that it must be from some inherent defect of the method of a fundamental kind."

In the Purvis lecture, on The Treatment of Inoperable Cancer, given before the West Kent Medico-chirurgical Society on December 6, 1912, Sir Alfred Pearce Gould,[3] has this to say of the X-ray: "By the use of X-rays in cancer of the breast I have seen foul ulcers cleaned, and some ulcers healed up entirely; I have repeatedly seen small secondary nodules in the skin and fascia disappear; I have had several cases when larger and deeper secondary growths, involving muscle, ribs, rib-cartilages, or sternum, have disappeared, and in other cases such growths have remained stationary and quiescent for such long periods that I could only think the radiations had had at least an inhibitory influence upon the growth. But in view of the extreme and remarkable natural variations that occur in cases of cancer, apart altogether from treatment, I desire to speak with great reserve upon this point."

Röntgen rays have been employed in conjunction with other agents (see Fluorescent Stimulation, page 291), and other methods (see Thermo-radiotherapy, page 317), in the treatment of cancer.

[1] Schultz, F.—"The X-ray Treatment of Skin Diseases." Trans. by James Burnet, New York, 1910.

[2] Jones, Henry Lewis.—"Medical Electricity," London, 1906, 5th ed., p. 373.

[3] Pearce Gould, Sir Alfred.—*Archives of the Roentgen Ray*, March, 1913, Vol. 17, p. 399.

RADIO-ACTIVITY

RADIUM

Sir Malcolm Morris, in the preface to the English edition of Wickham's book [1] (the first treatise on radium therapy), expressed an opinion parallel with that voiced by Adams in 1792: "The medical profession is as eager as were the Athenians of old to hear of any new thing; and it is somewhat prone to welcome a therapeutic novelty with excessive enthusiasm, and, when the inevitable reaction occurs, to dismiss it with perhaps undeserved depreciation."

"To this general rule of the formation of medical opinion," he continues, "radium has been no exception. On the strength of some exaggerated statements it has been hailed as the long-expected cure for cancer; and the notion of radio-activity has inflamed some minds to a degree far beyond anything for which the facts so far ascertained afford justification. It is scarcely too much to say that, but for the judicial temper brought by Dr. Wickham to the study of the problem, radium, whatever potency of healing it holds in itself, would have been relegated, as other remedies have been, to the limbo of charlatanism."

The words of Morris are particularly pertinent just now, in view of the recent widespread interest in radium in the United States. So much has been said concerning the matter, in both the medical and the lay press, that it needs no elaboration here.

After the discovery of the X-ray, in 1895, Becquerel, acting upon a suggestion of Poincaré, demonstrated the presence of penetrative rays in salts of uranium. Mme. Curie carried on the experiments, and in 1898-1900 isolated two radio-active elements from pitchblende (oxid of uranium), which she named polonium and radium.

Radium emits three kinds of invisible rays—*alpha, beta,* and *gamma,* and a radio-active gas called the emanation, which again splits up into other products, Radium A, Radium B, etc.

The *alpha* rays are easily absorbed, even by a sheet of writing paper. The *beta* rays are of different penetrative qualities, but the most penetrative are absorbed by about 2 mm. of lead. The *gamma* rays readily penetrate several inches of lead. The emanation possesses the activity of the radium itself, but has the disadvantage of losing its properties in a month.

The apparatus employed in treatment consists of: (1) Flat

[1] Wickham and Degrais, "Radium Therapy." Trans. by S. E. Dore, 1910. See also: "Radium and Cancer," London, 1913. Trans. by A. and A. G. Bateman.

varnish applicators for use in treating superficial lesions; (2) capillary glass tubes containing a radium salt and enclosed in a silver tube. These are mainly used in cavities or buried in malignant growths. (3) The emanation, collected in glass or silver containers. It may be dissolved in saline solution or distilled water and injected into the tumor. In any case suitable screens of aluminum, silver, or lead must be employed to filter out the irritant rays, viz., the alpha and soft beta rays.

Shortly after the discovery of radium, Danlos[1] made the first therapeutic researches with the substance. After a series of experiments, extending over three years, Danlos concluded that radium, employed wet or dry, exerted a curative action upon the majority of benign epitheliomata.

The pioneers in the therapeutic use of radium (Exner, Rollins, Béclère, Darier, Sichel, Williams, Krylov, Lassar, Follard, Repmann, Matzenstaum, Branstein, Mackenzie Davidson, Abbe, and many others) reported very few successes in the treatment of malignant neoplasms. Their many successes in the treatment of benign neoplasms did not counterbalance their failures with malignant growths, and so, despite some extravagant claims of cures, radium-therapy made little real progress until Wickham began his extensive investigations in 1905.

Wickham and Degrais,[2] in 1910, reported various degrees of improvement in the treatment of grave malignant neoplasms (1) in the skin and subcutaneous tissue; (2) in lymphatic glands; (3) in the breast; (4) in the buccal mucous membrane; (5) in the uterus.

In discussing the treatment of cancers in general by radium-therapy, these authors (p. 157) warned against conclusions based on cases which are few in number and which have been recently treated.

The most striking point in the investigations of Wickham and Degrais was that the results obtained were not confined to small epitheliomata, and were far better than those obtained by the first observers. "In lesions for which there is no hope of cure," they report, "it is sometimes possible to prolong the lives of patients, and to relieve their sufferings, even in cases where surgical, electrical, or X-ray treatment can no longer be employed with advantage. In ulcerating neoplasms one usually observes, in the first place, arrest of pain, hemorrhage, and discharge, and the disappearance of offensive odor; analgesia and diminution of congestion afford great relief in subcutaneous

[1] Danlos, H.—"Sur l'action physiologique et thérapeutique du radium," Bull. d. Sc. pharmacol., Paris, 1904, IX, 65-74.

[2] *Op. cit.*

neoplasms." "In growths of less serious character," they continue, "the improvement does not stop here, but is accompanied by other symptoms of resolution. Tissues are modified; the tumors become detached from their adherent bases, and diminish in size; vegetations subside and disappear; ulcers become cicatrised and gradually replaced by new tissues of excellent appearance. Subcutaneous neoplasms, in consequence of their fibrous transformation, frequently leave hard, indolent, and movable foci after treatment."

Successful results are reported by Wickham and Degrais in the treatment of tumors of various kinds—lymphadenoma, sarcoma, lymphosarcoma, and mycosis fungoides. Their efforts were not confined to malignant neoplasms which are easily accessible. Those which are accessible only with difficulty are not especially mentioned, examples thereof being recent, and their study still proceeding, yet some of the results obtained, they claim, are sufficiently clear and precise to permit them to assert the value of radium in a larger field than had hitherto been thought possible.

Dominici [1] suggested the idea of removing the injurious elements from the radium rays, meaning the easily absorbed *alpha* and *beta* rays. Although 90 per cent. of the total radiation is lost by this removal, the remainder is still strong enough for the accomplishment of various therapeutic effects. The technic is very simple: The source of the rays is surrounded by thin leaden plates (which exclude the harmful rays), which are encased in paper, to prevent secondary rays; the entire piece, which may be of any desired size, is then wrapped in a rubber sheet. This contrivance is either fixed on the outside, on the affected spot, or it may be introduced through a small incision into the interior of a tumor, where it may be left without interruption, up to 120 hours, or it may be removed and replaced at arbitrary intervals.

A series of cured cases were those of cancroids of the face, the nose, or the penis; carcinomata of the superior maxilla, the uterus, and the breast. Sarcomata, lymph sarcomata, and adenomata were also completely removed in this manner.

Dominici and Martel [2] endeavored to destroy carcinomata of the tongue by the introduction of small tubes containing radium, permitting only the passage of the ultra-penetrating rays into the core of the tumor. The technic is original and consists in

[1] Dominici, M. H.—"Du traitement des tumeurs malignes par le rayonment ultra-pénétrant du Radium," *Bull. de l'Assoc. Française pour l'étude du cancer*, Tome I, 1908, in *Revue de Médecine,* 1909, p. 124.

[2] Dominici and de Martel.—"Radiumthérapie du cancer de la langue," *La Presse médicale,* No. 18, 1910, p. 155.

transfixing the tumor and the tongue with a thick needle, which draws after it and places in position the radium-containing tube. Sometimes the radium-tube is inserted into a screw, which was especially constructed for this purpose, and the whole mass is slowly driven into the tumor.

This method of introducing the source of the radium rays into the center of the tumor had already been used by other investigators for various visceral tumors, but with rather imperfect and inappropriate instruments. The results obtained by these authors, however, were satisfactory, and consisted in softening of the tumor mass, cessation of the hemorrhage, and relief of pain, as well as a retrogression of the tumor.

Exner [1] reported four cases of cancer of the cheek and lips, not well adapted to operative removal, in which, by means of radium radiation, a cure was effected. That is to say, there was no recurrence for from two to seven years, up to the time of death from another cause, or until the time of the report. Exner especially emphasized the efficiency of radium treatment in certain cases with unfavorable prognoses.

In inoperable cases radium seems to have a distinct place of usefulness. Warden,[2] of Paris, reports cases which, in his estimation, warrant this conclusion.

Finzi [3] reported 117 inoperable carcinomata, not including cases of rodent ulcer, which were subjected to radium treatment, with the result that a complete local retrogression was obtained in 12 per cent., and relief of pain in 62 per cent. Radium should be employed, in his opinion, in all incurable cancers, also as a prophylactic measure after every cancer operation. Especially favorable effects are to be anticipated from large amounts of radium.

Finzi emphasizes the fact that the effect of radium is not confined to superficial growths, but may be obtained in deep growths, if care is taken to filter the rays in order to get the selective action.

1 Exner.—"Ueber Dauerheilungen von Karzinom nach Radiumbestrahlung," *Münch. med. Woch.*, 1910, No. 57, p. 2472.

See also: *Sitzungsber. d. K. K. Akad. Wissensch., Wien,* 1903, Vol. CXII, Abt. III, p. 285.

Exner and Holzknecht.—"Die Pathologie der Radiumdermatitis," *ibid.*, p. 155.

Exner.—*Wien. klin. Woch.*, 1904, p. 96; *ibid.*, p. 181. *Deut. Zeitschr. f. Chir.*, Vol. 75, 1905, p. 379.

2 Warden, A. A.—"Radium and Inoperable Cancer," *Brit. Med. Jour.*, 1913, Vol. 2, p. 1067.

Also: Dominici and Warden.—"The Technique and Results of Radium-therapy in Malignant Disease," *Brit. Med. Jour.*, 1910, Vol. 2, p. 516.

3 Finzi, N. S.—"The Radium Treatment of Cancer," *The Lancet*, May 20, 1911.

See also: Finzi, "Radium Therapeutics," London, 1913.

How this selection is brought about is not known. According to Finzi it is not due to anything actually introduced from the radium, the *gamma* rays being held to be "merely ether pulses and not material particles." "It has been suggested," he continues, "that the cells of a cancer are more easily damaged than the healthy cells surrounding them, and that any agent which injures the tissues will attack them first." He does not accept this view, calling attention to the fact that the *gamma* rays are much more powerful than X-rays in picking out the cells of the neoplasms, and infinitely more powerful than a simple irritant. Treated with radium (filtered rays), a growth can be made to disappear with no evidence of any inflammation.

When a full dose of radium rays, filtered through 1-1.2 mm. of lead or platinum, is used on the skin a double reaction is frequently noted; (1) an erythema, beginning about a fortnight after the treatment, and gradually fading away; (2) a pigmentation appearing about five weeks after treatment. The first is probably due to the *beta* rays which have escaped through the filter, and the second to the *gamma* rays.

Answering the question, "Does the absorption of a tumor have any effect on metastasis?" Finzi claims to have evidence that, in some cases, a metastasis may retrogress on the treatment of the primary growth or another metastasis. He is of the opinion that the destruction and absorption of the cancer cells should cause the formation of antibodies, and that these, in their turn, should lead to the destruction and absorption of other cancer cells.

With reference to the possible acceleration of growth of cancer cells under the selective action of radium, Finzi holds an affirmative opinion. In this connection he advocates the treatment of the whole growth thoroughly, as well as all outlying deposits of cancer.

The action of radium rays upon a malignant growth does not become apparent at once. The earliest changes noted by Finzi have been, a marked diminution of pain in one case, of swelling in another, and of fetor and discharge in others, occurring about one and a half days after the commencement of the application. These changes, together with the shrinkage of the growth, reach a maximum in four or five weeks. Toxemia, which occurs in many readily absorbed tumors, may be noted from the third day, generally lasting about two weeks.

The nature of the malignant growth, the position and size of the deposits, and the general condition of the patient, are all conceded to affect the successful use of radium. Some tumors, however small, fail to respond to radium treatment. This is particularly applicable to epitheliomata of the tongue and vulva.

The general rules laid down by Finzi for the application of radium radiations are: (1) treat thoroughly the whole tumor and the site of any possible metastases; (2) adequately filter the rays; (3) use as large an amount of radium as possible; (4) give maximum exposures.

The absolute minimum amount of radium bromid which Finzi considers efficacious in the treatment of cancer is 50 mg. He now uses 205 mg., with which amount his results are far more promising than with the minimum amount.

Edling [1] emphasizes that instead of the so-called massive doses (20-30 cg.) which are usually not available, smaller doses of radium salts (2 cg.), when applied for a sufficient length of time, seem to accomplish the same results. Four cases of inoperable carcinoma of the uterine cervix, in part, with involvement of vagina and rectum, were treated by the author in this manner. Two patients, aged 36 and 56 years, respectively, were apparently cured, being free from symptoms and without a tumor, at the end of six or seven months, respectively. Two other very far advanced cases were only temporarily improved.

A case of carcinoma of the uterus, with myoma, on account of severe hemorrhage and extreme anemia, was treated with radium, in preparation for operation. The hemorrhage subsided and, nine weeks later, a total extirpation was performed. Six months after the operation the patient was free from all symptoms.

In these cases Dominici tubes, with 2 cg. radium salt, of an activity of two millions, were inserted several times, at intervals, into the cervix, remaining for one week or longer. These tubes give off an ultra-penetrating radiation, composed of *alpha* rays and of hard *beta* rays; they must be placed in gauze-wrapped draining tubes in order to absorb the secondary radiation, which has an irritative inflammatory effect.

Ledoux-Lebard [2] strongly recommends the use of injections of sulphate of radium in inoperable carcinoma of the breast. The dose is from 5 to 20 micrograms, larger doses giving no greater relief. The injection is made *around* the cancer.

The London Radium Institute issued its first scientific report in January, 1913, covering a period from August 14, 1911, to December 31, 1912. During this time 657 cases, both

[1] Edling, L.—"Radium Treatment of Malignant Tumors of the Uterus," *Nordisk. Med. Arkiv*, 1911, Vol. 44, No. 16, p. 1.

[2] Ledoux-Lebard.—*Jour. de Radiologie de la Soc. Belge*, 1912, p. 205.

benign and malignant, were treated. The following table gives a summary of the results:

Summary.[1]

Examined but not treated	38
Recent cases, results not yet noted	41
Prophylactic irradiation only	39
Apparently cured	53
Cured	28
Improved	245
Not improved	70
Abandoned treatment	88
Dead	55
	657

There were 134 cases of epithelioma treated. Of this number 7 were apparently cured, 39 decidedly improved, 22 died, 20 showed no improvement, 23 abandoned treatment, 15 received prophylactic raying, and 8 were too recent to be classified. Of all the malignant conditions, rodent ulcer seemed the most responsive to radium irradiation. The Institute reports 101 cases, with 31 apparent cures and 12 uncured.

The histological changes which appear in secondary cancer nodules treated by radium have been studied by Dominici and Rubens-Duval, Delbert and Herrenschmidt, Hastings, MacCormac and Woodman, and others.

It has been estimated (Wickham and Degrais)[2] by Sir J. J. Thompson that the total energy liberated by a milligram of radium during its radio-active life would represent nearly a thousand million kilogrammeters, and Max Abraham has calculated that one gram of electrons (particles liberated in the course of the disintegration of matter) would represent the energy of eighty thousand million horse-power.

If these calculations be correct, it seems but reasonable to suppose that unless extreme care be exercised in the utilization of radium, this agent may be productive of more harm than good—that it may not only fail to retard malignant growth, but may accelerate it, and even cause its initiation. With this idea, in connection with studies concerning the action of X-rays, uranium and thorium, Lazarus-Barlow[3] investigated the effect of radium in the experimental production of cancer. He kept a glass tube containing radium in the abdominal cavity of a

[1] Pinch, A. E. Hayward.—"A Report of the Work Carried Out at the Radium Institute," *Brit. Med. Jour.*, January 25, 1913.

[2] See "Radium and Cancer," 1913, p. 7.

[3] Lazarus-Barlow.—"Radio-activity and Carcinoma: An Experimental Inquiry," The Croonian Lectures, *Brit. Med. Jour.*, June 19 and 26, 1909, pp. 1465 and 1536.

rabbit for months. Rabbits' ears were exposed to the rays for prolonged periods, under different conditions. The results were negative as regards the production of cancer.

MESOTHORIUM

It has been said: "Although radium itself remains at famine prices, its literature is increasingly abundant. We extend vain hands of supplication for milligrams and are given—a library." This state of affairs has led to many investigations looking to the discovery of a radium substitute which would be within the reach of a larger number of clinicians, while giving equal or better results in the treatment of disease.

With this end in view, Hahn [1] has worked with radiothorium, in an endeavor to separate it from the thorium minerals. Radiothorium, which emits *alpha* rays, loses half its activity in two years. Hahn found that the *alpha-ray* activity of thorium, after separation, decreased at first for some years, then slowly increased again to the activity of a pure thorium compound. From this he concluded that there must be another product in thorium which is transformed into radiothorium. He called this supposed product mesothorium. The half value period of this substance is about five and a half years. Mesothorium does not emit *alpha* rays, but is transformed into radiothorium, which does emit them.

Czerny and Caan [2] investigated the treatment of malignant tumors with mesothorium and thorium X. Their therapeutic experiments comprise altogether 120 cases, including 85 carcinomata, 12 sarcomata, 8 lymphosarcomata, 1 endothelioma, 6 angiomata, and 8 cases of tuberculosis, lupus, and other conditions.

In about 40 to 50 per cent. of the cases a favorable effect of the mesothorium, or the thorium X, respectively, upon the tumors was demonstrable. This effect, although sometimes rather inconsiderable, appears nevertheless noteworthy. The clinical material consisted, almost without exception, of well-advanced cases, in which no cure, but only a slight improvement, was to be anticipated.

The experiments would seem to show that mesothorium is at least equivalent to radium, and probably superior to it in the treatment of superficial tumors.

[1] Hahn, O.—"Ein neues radioaktives Element, welches Thoriumstrahlung aussendet," *Zeitschr. f. physiol. Chemie*, Leipzig, 1905, LI, 717. Translated (abstract) *Chem. News*, London, 1905, XCI, 193.

[2] Czerny and Caan.—"Ueber die Behandlung bösartiger Geschülste mit Mesothorium und Thorium X," *Münch. med. Woch.*, 1912, No. 14, p. 737.

Pinkuss[1] could not demonstrate a positive curative effect in 14 cases of cancer, either from ingestion, or local or intravenous injection of thorium X. More tangible effects followed upon local radiation with mesothorium-containing capsules. His observations concerning the action of mesothorium upon cancer were not complete, and no cured case could be placed on record. However, he suggested the use of mesothorium radiation as an adjuvant of operative measures, or as a substitute, when surgical interference is impossible. Mesothorium radiation is equivalent to radium radiation. It is superior to Röntgen radiation with reference to the deep action, the "dosibility," and the mode of application.

The most remarkable results with radium and mesothorium are those described in treatment of carcinoma of the uterus by Bumm.[2] He gives a brief description of a series of cases greatly improved, and clinically cured at the time of writing. It will be noted, however, that sufficient time has not elapsed to justify the use of the word "cure." Pearce Gould[3] recently described some remarkable immediate results, but in a later letter[4] in the same journal he stated that in two of the most striking cases the improvement had not been maintained, recurrence had taken place, and a lethal issue was in sight.

Finally, newspaper readers on both sides of the Atlantic are familiar with the recent sensational statements regarding the huge amount of radium deposited in a growth of the shoulder of a well-known Congressman, but which were followed later by the news of his death.

RADIO-ACTIVE GELATIN

Various radio-active substances have been utilized in the treatment of cancer. Particular attention has been given by some to radio-active gelatin, introduced into the region affected by a malignant growth after its removal, for the purpose of preventing recurrence.

It may be well, in this connection, to note that radium and radio-active substances furnish a prolific field of action for quacks.[5]

[1] Pinkuss, A.—"Zur Mesothoriumtherapie bei Krebskranken," *Berl. klin. Woch.*, 1912, No. 20, p. 935.

[2] Bumm, E.—"Ueber die Erfolge der Röntgen- und Mesothoriumbestrahlung bei Carcinom der weiblichen Genitalen," *Berl. klin. Woch.*, 1913, pp. 1001 and 1033.

[3] Pearce Gould, Sir Alfred.—"An Address on Radium and Cancer," *Brit. Med. Jour.*, Jan. 3, 1914.

[4] *Ibid.*, Jan. 24, 1914.

[5] *Nature*, April 30, 1913.

In view of the large number of drugs, earths, and waters, said to be radio-active, being offered for sale to the general public for the treatment of certain diseases, the Medical Committee of the British Science Guild recently instituted an inquiry into the question of radium and its therapeutic uses.[1] The result of the inquiry indicates the urgent necessity for legislation in order to safeguard the interests of the community by compelling a written guaranty to be given as to the quantity of radium present in the substances offered for sale.

The proposed inclusion of radium in the Pharmacopeia would be of material benefit to the public. It has also been suggested that radium should be scheduled as a poison under the Food and Drug Act. This would be an additional safeguard to the public.

ELECTROCAUTERY (Byrne Method)

The electrocautery, as introduced by Middledorpf, of Breslau, crude as it was, was considered by many surgeons as preferable to destructive chemical agents in the treatment of uterine cancer. Conspicuous among its advocates was the late Dr. John Byrne, of Brooklyn, who so adapted and improved the method that it has come to be known as the Byrne method of electrocauterization.[2]

Byrne considered the method absolutely free from danger, and claimed that it has secured for sufferers a period of exemption from relapse far beyond, and in startling contrast to that of hysterectomy.

The procedure as described by Byrne is as follows: First, all softened and broken-down tissue is removed by the free use of a *sharp* curet. The cavity is repeatedly sponged with a mixture of one part of commercial acetic acid, three parts of glycerin, and carbolic acid sufficient to represent eight per cent. of the whole, then packed with absorbent cotton, which is allowed to remain for a few minutes or longer as the case may be. On removing this, if all bleeding is found to have ceased, and

[1] The report of this committee will be published later.

[2] Byrne, John.—(1) "Vaginal Hysterectomy and High Amputation, or Partial Extirpation by Galvano-cautery in Cancer of Cervix Uteri. An Inquiry into Their Relative Merits," *Brooklyn Med. Jour.*, November, 1892.

(2) "A Digest of Twenty Years' Experience in the Treatment of Uterine Cancer by Galvano-cautery," Trans. Am. Gyn. Soc., Vol. XIV, p. 91.

(3) "Rules to Be Observed in Performing High Amputation and Other Operative Measures for Cancer of the Uterus by Galvano-cautery," *Brooklyn Med. Jour.*, November, 1892; also: International System of Electrotherapeutics.

the cavity is dry, cauterization may be proceeded with. If, however, oozing of blood to any extent should continue, it will be best to pass into the cavity a properly rolled tampon saturated with the above styptic, which should be allowed to remain for forty-eight hours before the application of the cautery.

The cauterization is carried out in the following manner: The diseased organ is exposed to view, and the vagina properly protected. Before introducing the cautery electrode a wad of absorbent cotton is passed into the cavity, held for a moment, and immediately, on being withdrawn, the cautery, which is brought to a cherry-red heat, is rapidly and repeatedly passed over *the bottom* of the cavity. The cavity is then again dried, and cauterization resumed as in the first instance. This process is repeated over and over until the deeper parts of the cavity have become dry and charred. The sides are then treated in precisely the same manner, and *roasted* to the same crisp condition. All ragged and overhanging edges are next trimmed off by the cautery knife. The cavity is then firmly packed, and a supporting vaginal tampon inserted.

After this preparation the high-amputation is executed as follows: "A circular incision is made, the cautery-knife, which is slightly curved, being introduced *cold,* and applied close up to the vaginal junction. The current is turned on from this instant, the knife is kept in contact with the parts being incised. Current cut off before electrode is removed for any purpose. Circular incision having been made to depth of say ¼ inch, by directing the knife upward and inward the amputation may be carried to any extent."

The metallic parts of the electrode for about two inches are covered with thin flannel to protect the vagina.

The advantages of the method, as stated by Byrne, are as follows: "(1) Absolute freedom from danger, immediate or remote, and (2) a longer respite from recurrence of the disease than has yet been shown by the most favorable and ingeniously constructed statistics of hysterectomy."

Despite the success which Byrne reported, and despite the occasional reported success of others, the method seems to have received no definite recognition from the surgical world.

Frederick [1] has recently reported the successful use of the method for five years. He also suggested the use of the cautery, not only as a means of preparing a limited number of these patients for later radical operation, in accordance with

[1] Frederick, Carlton C.—"Use of the Cautery in Treatment of Carcinoma of the Cervix," *Jour. Am. Med. Assn.*, January 14, 1911, p. 94.

Byrne's idea, but to prevent fresh infection of the raw surfaces at the time of radical operation.

Massey says,[1] in commenting upon Frederick's paper: "This paper of Dr. Frederick's is a belated tribute to the late Dr. Byrne, who is too little known as a member of the Royal Chirurgical Society of Edinboro, former president of the American Gynecological Society, and author of the section on Electro-thermal Surgery in the Bigelow-Massey 'International System of Electro-Therapeutics.' It is a sad comment on contemporary surgery, and its tendency to a blind adherence to prevailing fashions, that the radical teachings of this forceful man were absolutely neglected during his lifetime."

In my own experience the number of cases in which the Byrne method is indicated has been lessened by the Wertheim method, arterial ligation,[2] and other measures for the treatment of uterine cancer.

Percy [3] has reported the use of the electrocautery, basing his application of this agent upon the "time-immemorial fact" that high degrees of heat retard malignant growths on the surface of the body, as demonstrated by Leo Loeb,[4] Lambert,[5] and others. He has applied his method in inoperable cases in which he considers that either the Byrne or the Ries-Wertheim operation would be "utter foolishness." One of the benefits which he emphasizes, following the application of heat, is the apparent lessened virulence of metastases.

HIGH-FREQUENCY CURRENT

It would be impossible, in a work of this character, to enter into details concerning the different electric currents and the various methods of applying each. Among them great prominence has been given to the high-frequency current, which is now being so variously employed in the treatment of malignant neoplasms.

Credit is accorded to Rivière, of Paris, for inaugurating the

[1] Betton-Massey, G.—"Gynecology and Electro-chemical Surgery," *Journal of Advanced Therapeutics*, March, 1911, p. 139.

[2] See "Arterial Ligation" (Section XI, Chap. 2), and "Irremovable Cancer" (Section XII).

[3] Percy, J. F.—"A Method of Applying Heat Both to Inhibit and Destroy Inoperable Carcinoma of the Uterus and Vagina," *Surg., Gyn. and Obst.*, September, 1913, p. 371.

[4] See Percy.—"The Results of the Treatment of Cancer of the Uterus by the Actual Cautery, with a Practical Method of Its Application," *Jour. Am. Med. Assn.*, 1912, lviii, 696.

[5] Lambert, Robert A.—"Demonstration of the Greater Susceptibility to Heat of Sarcoma Cells as Compared with Actively Proliferating Connective Tissue Cells," *Jour. Am. Med. Assn.*, December 14, 1912, p. 2147.

application of high-frequency discharge from a metal point with a current of sufficient energy to destroy living tissue. Following his lead, a number of methods now claim attention, the originator of each maintaining certain points of difference from the original and from other subsequent methods. The various methods are discussed briefly in the pages which follow.

ALTO-FREQUENT CYTOLYSIS, ALTO-FREQUENT SCINTILLATION, EFFLEUVATION, ETC. (Rivière)[1]

The Rivière method of treating malignant tumors by high-frequency sparking and effleuve was first described in 1900. The term fulguration, he declares, was subsequently applied to the method, but not accepted by him as a designation for it. His conclusions at that time were that "high-frequency currents appeared to cure small facial epitheliomata and to exercise, in certain cases, a beneficial influence on the evolution of some malignant tumors. *They first produce a thermo-electrical-chemical action, the effect of which is to eliminate neoplastic tissues and, if we admit the parasitic theory, to destroy micro-organisms and their toxins; and, in the second place, they produce a tropho-neurotic curative action, which brings back the vital processes to the normal state.*

"It could not be a contemplation to employ the thermo-electrical-chemical action for the elimination of large tumors, for which excision is the elective treatment, but the surgical operation should be followed by the preventive and curative treatment in recurrent cases.

"High-frequency currents and, more especially, the monopolar effleuves of Oudin's resonator, seem to exercise this action by modifying the vitality of the new regions contaminated by the surgeon's knife during the operation, after having drained and disinfected them. This special mode of applying electricity seems, at the present time, one of the only therapeutical methods to be tried in cases of inoperable tumors."

Rivière reviewed the subject in 1909, asserting that since 1900 he had maintained that "every operation for malignant growths should be *immediately followed by the application of high-frequency sparks and effleuves,* in order to avoid contam-

[1] Rivière, J. A.—"Action of High Frequency Currents and of the Effleuves of Oudin's Resonator on Certain Malignant Tumors and on Tuberculosis," First International Congress on Medical Electrology and Radiology, Paris, 1900.

Also: "Alto-Frequent Cytolysis of Cancer."—*Jour. of Advanced Therapeutics,* 1909, pp. 337, 380, and 434.

Also: "Esquisses Cliniques de Physicothérapie—Traitement rational des maladies chroniques," Paris, 1910.

ination of the *open surgical wound* and to prevent recurrence." He declared that by means of different electrodes he could pass from the very finest shower of sparks (effleuves) to well-nourished short sparks (4 to 5 centimeters), and even to sparks and effleuves of from 5 to 15 centimeters in length. He insisted that the method of de Keating-Hart, to which the term fulguration has been applied, had added nothing to the Rivière method except the "useless spraying, or blowing, of air" through the electrode. (See Fulguration, p. 313.) Rivière did not agree that the high voltage claimed for the de Keating-Hart method was correct, but that on the contrary the voltage was low and the amperage high, just as in the Rivière method.

"DESTRUCTIVE FULGURATION"

The term "destructive fulguration" is sometimes employed to designate the method as usually employed by Rivière, and as it has been used by many surgeons and electrotherapeutists, viz., the destruction of malignant neoplasms by means of currents of high frequency, with short, low-tension sparks. To this method is frequently applied the term electrocauterization, or "burning down." Destructive fulguration has been very frequently confounded with the fulguration method of de Keating-Hart, which is in no sense, according to its originator, a destructive or burning method.

FULGURATION (de Keating-Hart)

One of the world's greatest philosophers has said: "There is a principle which is a bar against all progress, and which cannot fail to keep a man in everlasting ignorance; this principle is contempt prior to examination." It is the desire of every seeker after truth to avoid this deadly principle, to examine first, and then to accept with approval, or to reject with contempt. If examination is impossible, suspended judgment is in order.

The Committee on Scientific Research of the New York Skin and Cancer Hospital has borne this principle in mind in its study of the cancer problem, being willing at all times to investigate the claims of any method for the palliation or cure of malignant neoplasms, providing, of course, that such investigation presents no element of danger to the well-being of the patient concerned.

Accordingly, when, about five years ago, our attention was first directed to the treatment of cancer by the de Keating-Hart method of "fulguration," or "sideration," as it was then called, it was decided to investigate the theory upon which it was based, as well as the technic of its application, and, if results warranted it, to give the method a scientific trial in a series of cases.

During various trips to Europe, I visited Dr. de Keating-Hart, who demonstrated his apparatus and explained his method in detail. I saw him employ fulguration in numbers of cases, and examined many of the patients previous to operation, as well as upon successive visits afterward.

In some of the cases the cure of the cancer does not offer in itself any special interest, since this might have been obtained, as de Keating-Hart has pointed out, at least in the first group, by a number of well-known means. The cases are of real significance only when considered from a triple point of view:

(1) The strictly limited eradication of tissue around the lesions, thus saving or lessening subsequent deformity.

(2) The non-recurrence obtained for a number of years, although in certain cases the disease had not been checked by other means; or, in primary cases, the lessened likelihood of recurrence.

(3) The relatively slight disfigurement produced by the method in the cases presented.

These cases are all a matter of record, and are reproduced here merely for purposes of interest and emphasis. It may be said, in justice to de Keating-Hart and his method, that these cases represent patients of sufficiently varied ages and disease of sufficient severity to give to them an undeniable value. Each has undergone careful histological examination, and in the published works of de Keating-Hart may be found the names of physicians and surgeons by whom the patients were treated, as well as the names of the laboratories where microscopic examinations were made.

As the months passed and de Keating-Hart's reports continued favorable, as did likewise those of a number of other European investigators, our interest was still further aroused in the method.

Desplat, appointed by the French Association for the Advancement of Science to report upon "the remote results of fulguration in the treatment of cancer" (Congress at Toulouse, August, 1910), cited a number of interesting cases published by Dubois-Trépagne and himself. He concludes his report with the following: "After three years' experience, I conclude, as I concluded after the first year: that fulguration has enlarged considerably the field of surgery in giving it marked chances of success in those cases where it previously dared no longer intervene, and I now reply positively to the question which I had left under judgment for two years, that fulguration gives the patient chances of prolonged non-recurrence superior to those chances which surgery gives when left to itself alone."

Segond, who declared himself, at the International Conference on Cancer in Paris, in October, 1910, as being against the method, said of it, fulguration "has increased their resistance and prolonged their lives, transformed or cicatrized, in praiseworthy fashion, horrible, bleeding areas which tortured" patients whose pain nothing would calm. "Fulguration," he said, "permits surgery to intervene where intervention was no longer possible, and may offer a chance of non-recurrence to those cases which surgery alone cannot relieve."

Such statements, reinforced by our own observations, encouraged us, despite the unfavorable reports which from time to time appeared, to install a de Keating-Hart fulguration apparatus at the New York Skin and Cancer Hospital, and to extend to Dr. de Keating-Hart an invitation to visit New York and personally demonstrate the apparatus and explain the theories upon which his method of fulguration is based.

The apparatus, which had been constructed under Dr. de Keating-Hart's personal direction, was installed in the hospital in November, 1911, and in December he visited America, giving a series of demonstrations at the New York Skin and Cancer Hospital, and delivering a number of lectures in other cities. Invitations were extended to many of the leading surgeons in this country and Canada to attend these demonstrations, and the operating room was taxed to its utmost capacity each day by members of the medical profession who seemed eager to witness the fulguration "séances," as the originator of the method is wont to call the applications of fulguration.

Many cases of cancer, in various stages of operability, were treated during the nineteen days of Dr. de Keating-Hart's visit. The surgical operations were performed by the author, with the assistance of Dr. Franz Torek, Dr. E. M. Foote, and other members of the hospital staff. Dr. de Keating-Hart was assisted in the instrumentation by Dr. Worthington S. Russell, in charge of the electrotherapeutic department of the hospital.

Instrumentation and Technic.—The production of fulguration sparks may be accomplished by means of very differently adjusted apparatus. The following list comprises the equipment to which de Keating-Hart gives preference:

(1) Electric source: city current, dynamos, or accumulators, etc.

(2) A table holding the rheostats, amperemeters, etc.

(3) A transformer coil with rapid interrupter, or transformer in the closed magnetic circuit (alternating current).

(4) A condenser furnished with a spark gap.

(5) Oudin's resonator.

(6) A bellows furnished, according to the case, with a foot-pedal, or with a tube of carbonic acid, or an electric bellows with disinfected air.

(7) Special electrodes of de Keating-Hart.

(8) An operating table of wood or metal.

A few details to be emphasized:

(1) The source of the current must be powerful.

(2) The amperage at the primary may vary enormously (from two to eight or ten amperes, according to the voltage of the current, and the manner in which it is utilized by the internal construction of the coil, etc.).

(3) The length of the coil cannot be measured in terms of the length of the spark, as formerly, because of important modifications which have been introduced in the internal adjustment of the new apparatus. In the old models one was able to estimate a minimum of forty to forty-five centimeters of spark as the limit of the secondary. But the ensemble of the apparatus ought to be able to produce, at the extremity of the solenoid of the resonator, crackling white sparks of a minimum length of from seven to eight centimeters.

(4) The electrode, the special instrument for delivering the spark to the patient, is in the form of a sound. It is made of a smooth, metallic mandrel, or obturator, working snugly within an insulated tube of hard rubber.

(5) The bellows produced during the operation a constant circulation within the hard rubber tube of a current of carbon dioxid, or, preferably, of air, the purpose of which is twofold: 1, to prevent a rise in temperature of the column of air within the electrode where the sparks are produced; 2, to remove the coagulable liquids which may obstruct the free end of the sound at points of contact of the latter with the operative field.

(6) This gaseous circulation first strikes the upper end of the sound and escapes at the tip. An electric contact is then established between the electric source and the metallic mandrel. The mandrel is then withdrawn from ten to twelve centimeters outside of its hard rubber casing, in such a way that the point of the conductor is situated at an equal distance from the tip of the insulated sound. Consequently, in order to reach the fulgurated zone, the spark must pass through the non-conducting aerial column in the sound, which will permit the operator

to deliver sparks to those parts only which it is intended to reach. For a large, flat surface, such an instrument may not be necessary. In all hollow places, or in all empty organs, a spark which is not thus surrounded by insulation spends itself upon the edges or upon certain points and cannot penetrate in its entire length to the bottom of the place in question.

(7) Even with this instrument, perfected as it is, one is not free from all error of technic unless it be utilized according to certain principles and with extreme care. The first precaution is the surveillance of the proper functioning of the apparatus. If the interior wall of the hard rubber tube is still moist after being sterilized, it may change completely the properties of the spark, especially its length, by prolonging the metal conductor through a conducting liquid as far as the inferior extremity of the instrument. Likewise, it may happen that, in spite of the bellows, or, at least through its insufficiency, a coagulum may fill up the interior of the electrode, altering the force and the quantity of the current.

It would take too long to discuss here all the incidents which may take place in the course of fulguration, and, by changing the entire conditions, vitiate the results. From the foregoing it may be readily inferred that precision of technic is quite as essential in the application of the electrical current as it is in the preceding surgical operation.

Surgical Technic.—The first step of fulguration is purely surgical. This depends entirely upon the exigencies of the case, and need not be given detailed consideration here. Fulguration is essentially a method of treatment for *operable* cancers. The more complete the removal of diseased tissue, the more certain, according to de Keating-Hart, is the freedom from recurrence. The possibility of complete cure and absolute prevention of recurrence is commensurate with the extent to which eradication may be carried. Where only partial removal of diseased tissue is possible the method of fulguration is palliative rather than curative. In these cases de Keating-Hart advocates another method—thermoradiotherapy (see page 317.

Electrical Technic.—The electrical technic is simple in its description and delicate in its application. The general rule laid down by de Keating-Hart is as follows: Spark for a long time, using powerful sparks of high frequency and high tension, applying them to the area from which every macroscopic trace of cancer has been removed. It is, then, *under* the cancer, and not *upon* it, that the electrical discharge is applied.

The spark should be white, producing the sensation of a violent shock, its mean length to be from ten to twelve centimeters. An important detail is the utilization of the spark at its maximum length. The electrode should be kept in constant motion, and should be regularly passed over the surface being treated. The reason for this is twofold: (1) In order to avoid carbonization of the points at which the spark strikes the tissue; (2) in order to equalize the dosage, save at suspected points where one must work energetically.

It is impossible to establish the dosage, or the duration of the application of the spark upon a given point, in other than an empirical manner. It is not difficult to comprehend the reason for this, when one realizes that no two machines are exactly alike, and that in the same apparatus there may be great variations in the primary current, the distance of the spark-gap, and the conductibility of the air which surrounds it, all of which have an influence, as does likewise the insulation of the patient. Under such conditions the electrical properties of the spark are subject to enormous variation. As a general rule, however, one may advise "ten minutes of fulguration for an area of ten square centimeters." This is near enough for ordinary purposes, in the majority of cases, and with the usual apparatus.

Another guide in the matter of duration is the change in the color of the tissue being fulgurated. All tissues take on a slightly darker tinge, not from destruction, but from the deposit of small blood clots produced at the surface through contact with the spark. This change of color varies with the tissue involved. While the muscles take on the tinge of smoked meat, the bones become slightly yellow. In reality these appearances are apt to be deceptive, depending upon the manner in which the sparking is carried out, and upon the thickness of the sanguinolent fluid through which it passes. As a rule, bones should not be fulgurated as long as the muscles, or the vessels as long as the tendons.

The two main points to be emphasized are: (1) Sufficient removal of diseased tissue; (2) powerful sparking of the underlying tissues.

The method should not be condemned unless these two essential features are practiced. De Keating-Hart calls attention to the fact that most of the German authors, with the notable exception of Czerny, have published only failures. This is accounted for, in his judgment, by the fact that almost everywhere in Germany he has seen very defective electrodes employed. The apparatus in these instances permits of the use of a spark only about three centimeters long. Furthermore, this spark fails to affect the parts concerned when one is working at the bottom of a cavity.

Bad instrumentation and bad technic, combined with incomplete surgical intervention, are the chief causes of failure. In addition to these, an improper understanding of the indications for fulguration may lead to failure. Some tumors, because of their location (as in the intestines, uterus, brain, lung), escape the action of the spark. In such cases fulguration alone is not indicated, but "thermoradiotherapy," another method suggested by de Keating-Hart, of which we will speak later.

Theoretical Basis of Fulguration.—During the visit of Dr. de Keating-Hart to this country full notes were taken of his lectures and demonstrations, in order that our test of his method might be in absolute accord with his views. In addition to this, he was asked to formulate for us a full exposition of the theory upon which he bases his claims concerning fulguration. What is said here on the subject, therefore, is an abstract of his own statements. We wish to emphasize the fact that we are neither accepting nor rejecting his views, but that, as stated in the beginning, we are merely *examining* the evidence by clinical tests.

The premise upon which the de Keating-Hart fulguration method has been developed is that the *unipolar long spark of high frequency and high tension acts, not upon the neoplasms, but upon the soil on which the neoplasm has developed.*

Three groups of facts are relied upon to establish the premise.

(1) That sparking, even when used with inadequate surgical operation, gives undeniable results, insufficient, doubtless, but already very definite.

(2) That the tumor is in no way modified in its appearance or in its vitality, from which one may reasonably conclude that it is not the tumor itself, but the condition of its nutrition—that is to say, the environment in which it develops—that is transformed.

(3) That laboratory experiments and clinical observations furnish plausible explanations of the foregoing.

THERMOPENETRATION (d'Arsonval)

In 1896 d'Arsonval demonstrated the power of the high-frequency current to cause a decided rise of temperature in tissues interposed between two electrodes. This property of thermopenetration has been variously utilized by different investigators in the treatment of cancer. By some, notably de Keating-Hart, it has been employed for the purpose of heating the tissues with a view to rendering them more radiosensitive; by others (Nagelschmidt and Doyen) it has been used as a means of destruction of neoplasms.

THERMORADIOTHERAPY (de Keating-Hart)

The method to which its originator, de Keating-Hart, applied the term thermoradiotherapy consists, briefly, in sensitizing the tissues by fulguration, or other means, and their irradiation by means of X-rays, the skin surface through which the X-rays must pass being previously or simultaneously cooled in order to prevent X-ray dermatitis.

Theory.—De Keating-Hart's theory, upon which the method of thermoradiotherapy is based, is as follows: "Every luminous radiation passing through a living organism, determines in it biochemical reactions, the intensity of which varies with the quantity and duration of the exposure from a mere over-excitement of normal transformation to the destruction of cell-life. Such is the law regulating the relations of living beings to light, whatever the length of the luminous vibrations.

"It must not be overlooked, however, that a knowledge of the quantity, number, and duration of irradiations does not necessarily imply a knowledge of the length and intensity of biochemical reactions.

"The explanation of the unequal effects produced by radiations of the same strength must be sought in the morphological differences and the biological state of the cells themselves at the moment.

"Every radiotherapeutist, however expert he may be, and even with the use of the same instrumentation under the same general conditions, sees very different results according to the individual. It is well known that certain pathological tissues are much more sensitive than others to Röntgen rays.

"In 1907 Bergonié and Tribondeau (of Bordeaux) threw some light on these hitherto empiric notions. Their researches were made to determine the amount of cell destruction in the organic depths with radiations which were innocuous to surrounding or more superficial tissues. From their work these authors have arrived at certain conclusions which, if not sufficient to explain all known facts, permit one to understand at least many important phenomena.

"The following three laws are worth remembering: The activity of rays is proportional: *First,* to the reproductive activity of the cells; *second,* to the duration and constancy of their karyokinetic movements; *third,* to the higher differentiation of cell morphology and function.

"From these data we may readily conclude that the effect of X-rays on pathological cells is not specific. It is thus easily understood how neoplasms are destroyed by X-rays that pass through the more fixed normal cells. For the same reason certain tumors of rapid growth are more radiosensitive than tumors characterized by less constant and intensive karyokinesis.

"Of a similar nature are the conclusions drawn by Dominici and Chéron from radium effects. These experimenters not only observed a greater radium-fragility in the case of epitheliomata than in that of sarcomata, but they noted also the same difference between embryonic sarcomata and fibrochondro-sarcomata, tho cells and functions of which are more especially differentiated.

"In the same way also Schwartze observed that moistened and sprouting seeds are more radiosensitive than those which are previously dried. In this we have an obvious confirmation of Bergonié's findings.

"On the other hand, these laws do not by themselves explain the great skin-sensitiveness from which certain patients suffer during every exposure to X-rays, no matter how short the sitting may be.

"Furthermore, these laws do not explain the resistance offered to the Röntgen rays by certain tumors which were in the very beginning of treatment markedly radiosensitive. This is still more remarkable when we remember that cutaneous tissue becomes weaker at every successive radiotherapeutic sitting.

"Another contradictory fact was observed by Gerhartz: that the genital organs of frogs (organs, however, made up of karyokinetic cells) were not found to be sensitive to the X-rays. This would appear to be contrary to Bergonié's rule and to the conclusion drawn from Schwartze's experiments on seeds.

"Paul Becquerel, upon exposing dried spores of yeast, found that these spores are very quickly sterilized at normal temperature and but very slowly when frozen.

"When we consider that the experiments of Gerhartz were made during the winter on frogs, animals whose temperature is variable, we can only conclude that, as in Becquerel's experiments, cold seems to be opposed to the destructive action of rays on living cells.

"Histopathology, clinical researches, and personal experience have confirmed the statement that I made at the Dijon Congress, namely, *other conditions being equal, the radiosensitiveness of tissues depends upon their temperature.* In other words, the higher the temperature of tissues (between the normal vital limits) the greater the destructive power of radiation upon them."

Technic.—Thermoradiotherapy is applied in three ways, as follows:

(1) In the case of tumors with abundant blood supply, such as sarcomata, physiological hot serum is injected at 50° C., and in such quantity as to raise the internal temperature of the neoplasm to about 41° or 42° C.

(2) In cases of cancer developed in the natural cavities (rectum, vagina, stomach) irrigations as warm as possible are used during a time varying with the needs of the individual case.

(3) In tumors of a woody consistency, that can be heated neither by injection nor irrigation, high-frequency currents are employed either by passing the current through needles thrust into the skin, or through electrodes placed on the skin surface.

The last-named method of applying currents is not new. It has been employed by several persons, but with serious inconvenience, because, by rendering the skin more radiosensitive than the deep-seated tumors, they have produced radiodermatitis, making the subsequent application of the current impossible.

A natural consequence of the law controlling the relation of temperature to radiosensitiveness led de Keating-Hart to obviate the difficulty just mentioned by *cooling* the organs which he would protect. This is accomplished by several methods, two of which may be mentioned.

First, the surface to be protected by cooling is covered with cracked ice wrapped in cotton.

Second, a special apparatus may be employed which cools by blowing the dampened surface with a bellows.

Whenever possible, X-rays should be applied during the heating of the cancer, especially when the neoplasm is small and superficial. If the mass is deeply situated, as in uterine cancer, it may retain its warmth long enough for the irradiation to follow immediately after the warming process.

The irradiation must be subjected to the usual rules of radiotherapy. The longer and more frequent the exposures, without destroying the surrounding normal tissues, the more rapid are the local results. The results may sometimes be too rapid, which fact calls for great care, inasmuch as the cytolysis of the tumor may be the cause of serious autointoxication. This is particularly true of epithelial tumors.

Conclusions.—From a study of the data cited, and from his clinical observations, de Keating-Hart arrived at the following conclusions with reference to thermoradiotherapy:

(1) That the X-rays have a more intense action upon warmed than upon cold cells.

(2) That the application of this principle, by previously cooling the surface of the normal tissues to be traversed by the X-rays, produces more rapid destruction of the cancerous tissue with a weaker dose.

(3) That this treatment is applicable to the majority of cancers, but the autointoxication brought about by the cytolysis renders it advantageous to remove as much as possible of the cancer and to fulgurate the field of operation in operable cases.

(4) That in inoperable cases, and with patients who refuse all operative interference, thermoradiotherapy alone may be employed, care being taken to prevent too rapid cytolysis and consequent autointoxication.

(5) That cases in which the cancer has been completely removed and fulgurated show the same sensitiveness to X-rays as do warmed cancers.

DIATHERMY, OR TRANSTHERMY (Nagelschmidt)

In 1907, Nagelschmidt, in Berlin, and von Brendt, Preyss, and Zeynek, in Vienna, experimented independently with the thermopenetrative power of the high-frequency current. Since that time this method has been employed by surgeons in different centers, generally under the name diathermy, applied by Nagelschmidt. The apparatus employed permits the elevation of the temperature of the deep tissues to any required extent, the tumor being destroyed by the coagulation of the tissues. This is merely a thermic means of destruction, having no effect upon the trophic centers, or upon the soil upon which the cancer flourishes. It is claimed by its advocates that the tumor may be heated to the depth of 10 to 15 cm., and that the heat is dosable and localizable. Those who do not advocate the method hold that the cancer cells in the vicinity not reached are not destroyed, and that those which are reached, but not destroyed, are stimulated to heightened vitality.

Nagelschmidt [1] gave a practical demonstration of his method at the Dresden Congress in 1907. The essential high-frequency apparatus which he employs "consists of an undulatory electrical circuit, including a spark-gap, a capacity and a self-induction, in which electrical waves are produced by oscillatory discharges across the spark-gap. This is the principle of all high-frequency apparatus. The only differences are found in the construction of the spark-gap, the ratio of capacity to self-induction, with the addition of symmetric or asymmetric condensers and oscillatory circuits, induction or magnetic coupling, or secondary coils. It matters not whether we use as a spark-gap two metallic spheres, two metal plates, or the Poulsen arc, —or whether we use a constant or an interrupted current. The essential with all the above apparatus is the introduction of a more or less high-tension current, which is transformed into electrical undulations of high-frequency." The length of the waves may vary from 100 meters to several kilometers. The number of vibrations may be from 100,000 to many millions per second. The *damping* of the vibrations is the only important difference.

ELECTROCOAGULATION (Doyen) [2]

Doyen, after experimenting to determine the thermal death-point of cells, concluded that cancer cells are destroyed by a temperature of 122-131° F. (50-55° C.). Normal cells were found to be resistant up to 140° F. (60° C.). He employed the high-frequency current for the production of the thermic death of cancer cells, devising for the purpose a special apparatus. The cell destruction is the result of tissue coagulation, just as is the case with diathermy. At the New York Skin and Cancer Hospital, with the Doyen apparatus used for both electrocoagulation (Doyen) and diathermy (Nagelschmidt), it is possible to coagulate tissues to a depth of 5 to 8 centimeters in from one to two minutes. The apparatus produces a current of about three million oscillations per second, and of a strength of from 10 to 15 amperes. The active electrode is placed directly in contact with the tissue, thereby suppressing all sparks. The indifferent electrode is placed in contact with any part of the body, while the active is placed in direct contact with the lesion

[1] Nagelschmidt.—"The Thermic Effects Produced by High-Frequency Currents." (Report presented to the Third Congress of Physiotherapy at Paris, 1910.) *Archives of the Roentgen Ray*, Vol. 15, 1910-11, p. 58.
Also: "The Method of Diathermy in Medicine," *ibid.*, p. 132.
"Lehrbuch der Diathermy," Berlin, 1913.

[2] See General Bibliography.

to be treated. The current is allowed to pass for from 20 to 60 seconds. If this is not sufficient to coagulate the entire tumor mass, a second application may be employed. The slough separates in from ten to fifteen days.

At the Fourth *Congrès de Physiothérapie de Médecins de Langue Française,* held at Paris, April 9-11, 1912, Doyen confirmed the report of the successful treatment of all varieties of cancer which are readily accessible, by means of his method of electrocoagulation, without the use of the knife. He claimed to have had satisfactory results in cancer of the skin, lip, tongue, tonsils, pharynx, larynx, neck of the uterus, and rectum. He considered that the lapse of time and the experience of others with his method vindicated his claims.

BIPOLAR VOLTAIZATION (Doyen)

When the electrode of the Doyen apparatus is held away from the part to be treated, and the sparks are allowed to play upon the area, a superficial carbonization takes place, the underlying tissues being coagulated as when the electrode is placed directly in contact with the part, although not to the same depth. To this method Doyen applied the term bipolar voltaization.

OSCILLATORY DESICCATION (Clark)

According to Clark, heat effects range in degree from hyperemia to burning, and somewhere between these two extremes there is a point, the effect of which is more than hyperemia and less than burning, which may be called the desiccation point. His method of treating malignant neoplasms consists in the production, the control, and the maintenance of heat sufficient to cause rapid desiccation of the part to be treated, sterilizing and converting it into an inert mass. This is accomplished by a specialized, true oscillatory, high-frequency current, concentrated to a very fine metal point, and delivered in sparks of great frequency through an air space to the tissue. He employs a static machine with a large output (3 to 6 milliamperes).

Clark [1] concludes from his clinical investigations as follows: "A current from a static machine of large output with properly attuned accessories, when applied with correct technic and care, is capable of producing a superficial or a deep destruction of tissue by desiccation, or rapid depletion of its fluid elements, which breaks up and disintegrates the cells.

[1] Clark, William L.—"Oscillatory Desiccation in the Treatment of Accessible Malignant Growths and Minor Surgical Conditions. A New Electrical Effect," *Jour. of Advanced Therapeutics,* 1911, Vol. 29, p. 169.

"It has sterilizing, styptic, and stimulating properties.

"This specialized current has no particular affinity for abnormal tissue over the normal, but it is a simple matter to keep the destruction well within bounds on account of refinement of control.

"It is operative in all accessible lesions where destruction is desirable, and works from without inward.

"Living tissue is destroyed by this means almost as readily as dead tissue (raw meat).

"The rapidity of action appears to be directly proportionate to the density of the tissue."

This method is often referred to as fulguration. Fulguration, "as practiced at home and abroad for several years," according to Clark, "is not desiccation, the thermic degree being too high, and the impact against the tissue too severe." He doubtless refers to the so-called "destructive fulguration."

IONIC SURGERY

(Cataphoresis)

With the purely local origin of cancer as the basis of his theory, G. Betton-Massey has elaborated a method of treatment to which he has given the name *Ionic Surgery.*[1]

The requisites for any method in such cases are that it "acts as quickly and thoroughly as the knife in a favorable case for that method, and yet is capable of application through the growth itself, from within outward, enabling us to reach the actual periphery of the latter by a combined destructive and occlusive agency, devitalizing all cells *in situ* and sterilizing the outermost edge while, at the same instant, sealing the absorbents, thus effectually preventing operative reinfection."

According to Massey, and others who have followed his work, these requirements are met by the massive diffusion of the ions of mercury and zinc by powerful electric currents, as devised and developed by him.

Furthermore, that the diminishing density of the diffused ions will produce a zone of reaction beyond the area of total necrosis, thus destroying outlying latent cancer cells, and only arousing the physiological resistance of the normal tissues.

The method of Betton-Massey consists in the "utilization of the electrolytic and phoretic powers of a strong electric current for dissolving and ionizing zinc points or needles coated with mercury and thrust into the growth." By this means, and

[1] Betton-Massey, G.—"Ionic Surgery in the Treatment of Cancer," 1910.

with the patient anesthetized, it is claimed that a sufficient quantity of mercury and zinc may be interstitially diffused throughout a tumor in a few minutes to kill all malignant cells and their accompanying germs, should such be present.

By prolonging the process sufficiently the microbicidal substances will be driven farther than the apparent boundaries of the growth in strength sufficient to kill outlying colonies and lines of dissemination in the immediate neighborhood, without serious injury to the contiguous healthy tissues.

The physiological basis of this method of the ionic sterilization of diseased foci is the fact that living tissues, particularly such highly cellular and vascular tissues as malignant growths, consist of various salts in organic combination held in solution in water.

In a period of time varying from twenty minutes to one hour, according to the size and situation of the growth, with proper placement of the electrode, the whole of the apparent limits of the diseased tissues will be included in the area of necrosis. Both sight and touch determine the completeness of this effect. A change of color to grayish white is noted by the eye, and a distinct softening of the brawny induration is perceptible to the touch.

SUMMARY

Phototherapy.—The use of light in the treatment of cancer is mainly restricted to the alleviation of pain; beyond this it is of no real benefit, and has been generally abandoned for other methods.

X-Rays.—Without question the X-ray has a marked analgesic effect which lasts several days after an application, often thereby deceiving the patient into the belief that there is an improvement in his condition, and very materially aiding in inspiring an element of hope. Certain superficial growths, such as small squamous-celled carcinoma, can be made to disappear by the correct application of the ray, and in many cases the progress of a malignant growth can be stayed for a time. The permeation nodules recurring after operation will often disappear under irradiation, and a large adenomatous arm may diminish in size. In deep-seated cancer, however, the beneficial effect, when obtained at all, is temporary and palliative. On the other hand, growth may be accelerated and metastasis hastened. A new X-ray tube has been introduced called the Coolidge tube, which is constructed on a new principle, and which is capable, it is claimed, of producing very penetrating rays, simulating the *gamma* rays of radium. This tube gives promise of increasing the field of usefulness of the X-ray, but it has not been employed a sufficient length of time to establish its scope and limitations.

Radium, Mesothorium, and Other Radio-active Substances.—Radium and other radio-active substances have probably other than caustic or purely destructive effects. Radium may certainly be described as the most efficacious of all caustics, but in addition it has an effect on all growing tissues. This fact is the main justification for its use in cancer. Its field of usefulness is in the treatment of superficial lesions, such as rodent ulcer, and certain benign conditions, keloids, angiomata, nævi, verrucæ, etc., which can be cured. There is no evidence to show that radium has any but a palliative effect upon deep-seated cancer. It has been claimed by some that radium may in some instances convert an inoperable growth into an operable one. This is debatable. It is too early, however, to give a positive opinion as to the true value of radio-active substances in the treatment of cancer. The materials are being thoroughly tested in the various centers and by many individuals, the author among others. Whatever place of usefulness they may have can be determined only after a sufficient time has elapsed.

The combination of radiotherapy with surgery is very promising. Czerny believes that mesothorium is of more value in treatment than radium, but this has yet to be demonstrated. The words of Charles Ryall, F.R.C.S., Chairman of the Medical Committee of the London Cancer Hospital, are very appropriate at the present time: "It would be well if those who are experimenting with radium would be silent for the next couple of years until they know where they are, and can make some definite announcement. Radium has not come to supplant surgery in the treatment of cancer, but to aid it in fighting the disease."

The investigator, seeking to learn the value of radio-active substances in the treatment of malignant disease, after reading the many opinions in this chapter will readily conclude that, despite the extravagant claims made by some, the whole matter is in an experimental stage. We would emphasize that it is too early to determine the true value of these agents in the treatment of cancer. A better understanding of physics, and an improved technic, may lead to a fulfilment of some of the hopes with reference to these substances.

Fulguration, Electrocoagulation and Thermoradiotherapy.—During the past three years the author, with the assistance of Dr. Worthington Seton Russell, has employed these methods in over four hundred cases of all forms of malignant growths with some encouraging results which warrant a continued test. Fulguration, as has been stated in the text, is a post-operative procedure, and seems to offer in many instances more hope than surgery alone, although the radical removal employed may be the real beneficial factor and not the high-frequency electricity. It will take time and a careful comparison of results to settle the question of fulguration's place of usefulness. Our results in conjunction with thorough excision of all microscopic cancer are gratifying enough to warrant a continued trial. Electrocoagulation may be used with or without a surgical procedure, and is of decided benefit in cleaning up ulcerating masses. Thermoradiotherapy seems of benefit in inoperable cases. A detailed report of our work will be forthcoming in a short time.

Other Methods.—The various other methods given in this chapter have their advocates, but have not been accepted.

CHAPTER III

BIOTHERAPY

CLASSIFICATION OF AGENTS

For a decade or more attention has been very largely directed toward the treatment of cancer along biological or biochemical lines. In the majority of instances the method of treatment is founded upon a theory of the etiology of the disease. The theory failing of proof, the method has generally met with skepticism and discouragement, only the adherents of the given theory continuing the systematic employment of the correlated method of treatment.

The production of sera neutralizing the products of bacteria, and actually injurious to the bacteria themselves, has played an important part in therapeutic endeavors to deal with cancer.

The discovery that sera could be prepared which would dissolve red blood corpuscles in the test tube, and subsequently that kidney, liver, and other epithelial cells could be dissolved by injecting them into other animals, gave rise to the hope that, similarly, sera might be prepared having actions limited to special tissues. Naturally the possibilities of a biological therapy for cancer sprang into renewed prominence, in which it was sought to utilize the reactions of the living body, not against supposed organismal causes of cancer, but against actual cells. Therefore these measures fall into many groups, according as they are based upon bacteriology or upon the cytolysins or cytotoxins, but the confused use of the terminology of bacteriology in describing the cellular (cytolytic) endeavors, makes sharp separation impossible.

The various biological measures, however, may be considered under the general heads of:

(1) Serotherapy.
(2) Vaccine therapy.
(3) Opotherapy.

The confusion of phraseology with reference also to the various biological measures used in the treatment of cancer, renders it practically impossible to formulate a definite classification. The following terms are employed by the majority of writers with a degree of careless overlapping which too often characterizes medical literature:

(1) Bacterial toxins.
(2) Antitoxic sera.
(3) Antitoxins.
(4) "Toxins" or "Fluids."
(5) Vaccines.
(6) Residues, Extracts, and Emulsions.
(7) Serous exudates (Sera).
(8) Opotherapeutic measures.

An excellent illustration of this confusion of terms is furnished by the Coca-Gilman "Vaccine Emulsion," which is referred to by very nearly all the terms employed in the foregoing classification. Another illustration is the "Cytolytic Serum" of von Leyden and Blumenthal.

In the above list it is impossible to determine whether the authors would or would not agree that, by "bacterial toxins," "toxins," or "fluids," the same group of agents is meant. The same applies to antitoxic sera or antitoxins. Vaccines, residues, extracts, and emulsions may likewise, at the hands of one author, signify identical procedures, and at the hands of another, something different, owing to the one conceiving the existence of an intracellular cancer parasite and another entertaining only cellular conceptions.

DEFINITION OF TERMS

In view of this confusion it may not be amiss, particularly for the convenience of readers who have made no special study of the subject, to define briefly the various terms under which the biological treatment of cancer has been considered. It should be borne in mind that many of the procedures are really only haphazard experiments in treatment.

Serotherapy is the treatment of infective diseases by means of sera of immunized animals. It may be preventive or curative, or both. The animal furnishing the serum has produced its own immunity; in other words, it possesses active immunity which can be transferred to other animals by injecting its immune serum. The animal which receives such a serum acquires a passive immunity. It is readily understood, from what is known as well as from the lack of knowledge concerning cancer, how difficult it is to apply the ordinary bacteriological definitions to the treatment of this disease. In many cases they are carelessly so applied as the result of false analogies with the infective diseases.

Antitoxin; Antitoxic Serum; Bacterial Toxins.—An antitoxin is a substance in the serum which binds and neutralizes toxins. According to the side-chain theory of Ehrlich, it consists of *receptors,* which have been produced in excess, and which have been thrown off into the body fluids. In other words, an antitoxin is developed in the body as a result of the introduction of a poison, and acting as a neutralizer of that poison. Antitoxin has not been separated pure, that is, freed from all albuminous substances in the blood serum.

An antitoxic serum is one which contains the antitoxin of the pathogenic micro-organism, against infection by which it is protective or curative. A *specific serum* contains a large number of amboceptors (according to the side-chain theory) which have a special affinity for a given bacterium or the red cells of one animal in particular, and which serve to bind the *complements* (the active elements in lysis) in either specific or normal serum to these cellular elements, and so to effect their destruction.

Examples of antitoxins, antitoxic sera, and bacterial toxins which have been employed in the treatment of cancer are:

(1) *Blastomycetic antitoxic serum* of Sanfelice, based upon the theory that cancer is due to blastomycetes.

(2) *Wlaeff's Serum,* made from cultures of blastomycetes from cancerous growths, inoculated into pigeons.

(3) *Serum of Emmerich and Scholl,* made by inoculating sheep with *Streptococcus erysipelatosus.*

(4) *Doyen's Serum,* from *Micrococcus neoformans* (see Section IX, p. 256, "The Investigation of 'Cancer Cures' ").

(5) *Schmidt's Serum,* from *Mucor mucedo* (Cancroidin, Antimeristem). (See Section IX, p. 252, The Investigation of "Cancer Cures.")

(6) *Wyeth's Toxins of Streptococcus.*

(7) *Coley's Fluid*—Mixed toxins of *Streptococcus erysipelatosus* and *Bacillus prodigiosus.*

Vaccine; Vaccination.—A vaccine, as ordinarily understood, is the modified and attenuated virus of any disease, incapable of producing a severe infection, but affording protection, when inoculated, against the action of the unmodified virus. In the case of cancer the term is frequently used to mean an inoculation of disintegrated cancer tissue or even of normal tissue.

According to Coca,[1] "In relatively recent times the use of the term 'vaccination' has been extended to apply to the injection of killed cultures of pathogenic bacteria for the purpose of artificially inducing an active immunity against the living organisms. This procedure has usually been resorted to as a therapeutic measure during a subacute or chronic infection by the respective micro-organisms, sometimes, however, during an acute infection or as a prophylactic measure, such as in typhoid, cholera, and bubonic plague."

"If we inquire," he continues, "whether there are, in the literature dealing with the clinical and experimental study of malignant tumors, and with the study of tissue-cell immunity, any facts which might justify the application of the vaccination therapy to the treatment of malignant disease in human beings, we find that such facts do exist in abundance." By referring to Section VI, p. 161, under *immunity reactions,* it will be seen that the greatest experimental authors absolutely deny that there is any justification for Coca's statements regarding vaccination as he describes it.

Illustrations of vaccines used in the treatment of cancer may be found in:

(1) *Micrococcus Neoformans Vaccine* (Doyen), used in connection with the serum made from the same organism.

(2) *Bacterial Vaccine* (Jacob and Geets), made from *Micrococcus neoformans* cultures of the same age, sterilized, washed, and standardized according to the opsonic theory.

Residues; Extracts; Emulsions.—These are preparations of cancerous material or of normal tissue, to be injected hypodermatically. The different residues or extracts are referred to as sera or vaccines. Conspicuous examples of this class are:

(1) Coca-Gilman Extract, or Emulsion.
(2) Vaughan Residue.
(3) Fichera Emulsion.
(4) Autolyzed Cancer or Normal Tissue. (Pinkuss and Kloninger.)

Serous Exudates and Body Fluids (Sera).—Under this head come the various body fluids, normal and pathologic, which have been employed in the treatment of cancer. The following are examples:

(1) Hodenpyl's Ascitic Fluid from a cancer subject.
(2) Normal Blood Serum (human).
(3) Blood Serum (horse) (Strauss).

[1] Coca, Arthur F.—"Vaccination in Human Cancer in the Light of the Experimental Data upon Normal Tissue and Tumor Immunity," *Zeitschr. für Immunitätsforsch. u. Exp. Therapie,* 1912, Vol. 13, p. 524.

(4) Blood Serum (donkey) (Loeffler).
(5) Hydrocele Fluid.
(6) Spermatocele Fluid.
(7) Ascitic Fluid from the subject of alcoholic cirrhosis.
(8) Ascitic Fluid from the subject of cardiac insufficiency.
(9) Pleuritic transudate resulting from broken compensation.

Opotherapeutic Measures (organotherapy) consists, as the name implies, of preparations of certain organs or parts of animal or human bodies. Examples of agents of this class are:

(1) "Antituman" (Oestreich)—Embryological cartilage and arteries, from which is extracted chondroitin-sulphate of sodium, supposedly an immunizing substance.
(2) Thymus Gland Extract (Gwyer).
(3) Extract of Sheeps' Thyroids (Am Ende).
(4) Pancreatic Enzymes—Trypsin and Amylopsin—(Beard).

Among the various biological measures mentioned in the foregoing pages, the following are discussed in Section IX: "The Investigation of 'Cancer Cures'"; Pancreatic Enzymes (trypsin and amylopsin), p. 242; "Cancroidin" or "Antimeristem" (Schmidt), p. 252; *Micrococcus neoformans* Serum and Vaccine (Doyen), p. 256.

It is manifestly impossible, in a volume of this scope, to discuss the complete list of biological products which have been proposed in the treatment of malignant diseases. Nor would such a discussion be profitable, in view of the fact that many of the agents have been discarded, with practically a consensus of opinion against their efficacy; others continue to receive a certain amount of attention, largely because no definite test of their value has been made upon a convincing basis; while still others are being given careful consideration by a sufficient number of skilled clinicians to warrant the hope that a decision, *pro* or *con,* will be soon forthcoming.

The following agents are considered under the classification:
(1) Serotherapy.
(2) Vaccine therapy.
(3) Opotherapy.

For the benefit of those who may desire to study the subject more fully a fairly comprehensive bibliography is given.

A. BASED ON BACTERIOLOGY

SERA

(Bacterial Toxins)

Wlaeff's Serum (Blastomycetes).—In 1900 Wlaeff [1] claimed to have obtained from malignant tumors certain parasitic cells (blastomycetes), which had the power, when inoculated into the peritoneum of guinea-pigs, of producing abdominal cancer in these animals. His attempts at immunizing different animals proved successful only in pigeons, fowls, and geese, from which he obtained an active serum. He held that this serum, administered to rats previously inoculated with blastomycetes, prevented the development of cancer.

In his experiments upon human beings Wlaeff used a serum obtained from geese, 5 to 10 c. c. being given with each injection. In his own experience, when given early, before ulceration and glandular enlargement had occurred, the serum exerted a curative influence; when metastasis was present the serum improved the patient's general condition and prolonged life, but did not effect a cure.

Lucas-Championnière,[2] Berger,[3] and others have employed the serum, with no cures. In some cases, however, improvement was noted.

The injection caused considerable local and general reaction, but nothing more serious.

The method, so far as I am aware, has been abandoned.

The same may be said of the *Blastomycetic Antitoxic Serum* of Sanfelice.[4]

According to Ewing,[5] these agents, like the serum of Emmerich and Scholl [6] (*Streptococcus erysipelatosus*), Doyen's Serum (*Micrococcus neoformans*), and Schmidt's Serum (*Mucor mucedo*), may cause partial retrogression of a tumor, after

[1] Wlaeff, G.—"Serum anticellulaire." Compt. rend. Soc. de Biol., Paris, 1900, iii, 611-613.

[2] Lucas-Championnière.—Discussion of Wlaeff's Serum, *Bull. et Mém. Soc. de Chir. de Paris,* 1901, xxii, p. 174.

[3] Berger, Paul.—Discussion of Wlaeff's Serum, *Bull. et Mém. Soc. de Chir. de Paris,* 1901, xxvii, p. 174.

[4] Sanfelice, Francesco.—"Tossine ed antitossine dei blastomiceti patogeni in rapporte alla etiologia ed alla cura dei tumori maligni." Chap. IV, *Annali d'Igiene experimentale,* 1908, p. 521.

[5] Ewing, James.—"The Treatment of Cancer on Biological Principles," *N. Y. Med. Jour.,* October 19, 1912.

[6] Emmerich, R., and Scholl, H.—"Klinische Erfahrüngen über die Heilung des Krebses durch Krebsserum (Erysipelserum)," *Deutsch. med. Woch.,* 1905, XXI, 265-268.

which they are usually ineffective. "There is little doubt," he says, "that complete disappearance of malignant tumors has been observed in a small proportion of cases during the use of these agents." He agrees with Vidal[1] concerning the pyrogenetic nature of these poisons, i. e., that the effect on the tumor is usually proportional to the fever.

Wyeth's Toxins of Streptococcus.—Wyeth[2] reported three cases in which malignant tumors disappeared after septic infection.

Coley's Fluid (Mixed Toxins of *Streptococcus erysipelatosus* and *Bacillus prodigiosus*).—Of the various bacterial products which have been proposed in the treatment of malignant neoplasms the one which has attracted most attention is Coley's fluid. Inasmuch as it is based upon the curative influence of erysipelas, it may be interesting to review briefly the evolution of the method.

The beneficial effect of erysipelas upon concurrent disease is said to have been known to Hippocrates (460-377 B. C.). Definite observations upon the subject appeared in medical literature in the seventeenth century, and have grown gradually more frequent up to the present time. Syphilis, convulsions, epilepsy, mental diseases, neuralgia, typhus fever, acute rheumatism, asthma, lupus, and various other skin diseases, including malignant new growths, were thought to be mitigated or cured in certain instances by a concurrent attack of erysipelas.

Cazenave and Schnedel, in 1839, endeavored to induce erysipelas as a therapeutic measure in the treatment of skin diseases.

According to Fehleisen,[3] the discoverer of the germ (1883), and naturally a close observer of erysipelas from all points of view: "It is undeniable that many tumors have entirely disappeared by the action of erysipelas. Mistake is not possible as to this, because such degeneration of new formations does not otherwise occur. Many swellings of the skin, epithelioma, keloid, carcinoma of the mamma, and lymphatic gland enlargements of various kinds, have been partially absorbed as a result of an attack of erysipelas. The first attempt to employ

[1] Vidal, E.—Discussion (La résistance des cellules concéreuse, etc.), *Assoc. Franc. de Chir., 21 Congrès de Chir.*, Paris, 1908, p. 939. *Comptes rendus, 21 Congrès française de chirurgie,* 1908; II International Cancer Conference, 1910, p. 315.

[2] Wyeth, John A.—"The Value of Inoculations with Septic or Toxic Agents in the Treatment of Malignant Neoplasms," *N. Y. Polyclinic,* July 15, 1894; also *Jour. Am. Med. Assoc.*, XXII, 1894, p. 985.

[3] Fehleisen.—"On Erysipelas" (trans. by Leslie Ogilve, in Microparasites in Disease), edited by Watson Cheyne, p. 272.

erysipelas as a curative agent was made by Ricord and Deprès, who endeavored to reproduce artificial erysipelas in phagedenic chancres. With great zeal W. Busch [1] followed up the idea of healing, by means of erysipelas, malignant new formations of the lymphatic glands which were unsuitable for operation. He was successful in infecting a patient by placing her in a bed in which patients with open wounds usually became attacked by erysipelas. The desired result took place, and the swelling, which was an extensive lympho-sarcoma of the neck, disappeared all but a small portion, which, however, again enlarged. The result was thus only a partial one, but at the same time it encouraged further trials." The cases of Busch and Volkmann [2] convinced Fehleisen of the possibility of effecting a permanent cure.

The work of Fehleisen was followed by that of many others, notably Emmerich and Scholl,[3] Bruns,[4] Senn,[5] von Jaksch,[6] and Coley.[7]

The manner in which absorption of the tumor takes place through the action of erysipelas was not well understood by Fehleisen. Supposedly the cells of the tumor appeared to have undergone fatty degeneration, and were found to have been transformed into a "yellowish-white emulsion," as in one of the cases reported by him. The view has been expressed by subsequent observers that the high temperature produced during erysipelas acts upon the sarcoma cell.

Coley's [8] attention was first directed to the curative action of accidental erysipelas in inoperable sarcoma by a case which he observed in 1891. Among 90 cases of sarcoma analyzed by him at that time, which had been operated upon at the New York Hospital during the preceding fifteen years, was one of

1 Busch, W.—"Einfluss der Erysipele auf organisirte Neubildungen," *Berl. klin. Woch.*, 1866, p. 245.

2 Volkmann, R.—"Erysipelas," Billroth and Pitha.

3 Emmerich, R., and Scholl, H.—"Klinische Erfahrungen über die Heilung des Krebses durch Krebsserum (Erysipelserum)," *Deut. med. Woch.*, 1895, XXI, 265-268; *Sémaine médicale,* 1895, 220.

4 Bruns, P.—"Zur Kregsbehandlung mit Erysipelserum," *Deut. med. Woch.*, 1895, XXI, 313, 428; *Sémaine méd.*, 1895, 236.

5 Senn, N.—"The Treatment of Malignant Tumors by the Toxins of the Streptococcus of Erysipelas," *Jour. Am. Med. Assn.*, 1895, XXV, 129-131.

6 Von Jaksch, R.—"Ueber die Behandlung maligner Tumoren mit dem Erysipelserum von Emmerich-Scholl," *Mitth. a. d. Grenzgeb. d. Med. u. Chir.*, Jena, 1896, I, 318-327.

7 Coley.—See General Bibliography.

8 Coley, William B.—"The Treatment of Inoperable Sarcoma by Bacterial Toxins (The Mixed Toxins of the Streptococcus Erysipelatosus and the Bacillus Prodigiosus)," Proc. of the Royal Soc. of Medicine, July, 1909, Vol. 3, Part III, Surg. Sect., pp. 1-48.

round-celled sarcoma of the neck, four times recurrent. At the fifth operation, in 1884, the late Dr. William T. Bull found the tumor to involve the deep structures so extensively that removal was impossible and the attempt was abandoned, the case being regarded as absolutely hopeless. Shortly after the operation a severe attack of erysipelas developed on the man's face and neck, followed two weeks later by a second attack. A few days after the beginning of the first attack the tumor began to soften and decrease rapidly in size. When the patient left the hospital, according to the hospital record, the tumor had entirely disappeared. No further record of the case was filed with the history, but Coley succeeded in tracing the patient, and found him, seven years after the operation (1891), well, and with no evidence of local or general recurrence.

The experiments of Fehleisen were unknown to Coley at that time, but he was so strongly impressed by this case that he determined to try inoculation with the streptococcus of erysipelas in the first suitable case.

This opportunity presented itself in May, 1891, when he made his first inoculation in a case of recurrent spindle-celled sarcoma of the tonsil and neck. The history of this case is detailed in Coley's paper [1] on the subject.

During the next two years inoculations were employed in a number of chronic and incurable cases of malignant disease.

These experiments with living cultures convinced Coley that it is extremely difficult to produce erysipelas at will; that the risks of inoculation, when successful, are considerable, and that repeated injections of the streptococcus of erysipelas exert a distinct, though temporary, inhibitory action upon the growth of the tumor. He concluded from his observations that a portion at least of the curative action of the erysipelas lay in the toxic products of the disease, which might be utilized without producing an actual attack of the disease.

Accordingly, in 1892, Coley began his experiments with the toxins of erysipelas. He found the constitutional reaction to be very similar to that obtained from the living cultures. Then, in view of the experiments of Rogers with the *Bacillus prodigiosus,* showing that this organism, when grown together with the *Streptococcus erysipelatosus,* intensified the virulence of the latter, Coley decided to combine the toxins of these two organisms.

[1] Coley, William B.—"Contribution to the Knowledge of Sarcoma," *Annals of Surgery,* 1891, XIV, p. 199; also *Am. Jour. Med. Sciences,* 1893, Vol. CV, n.s., p. 487.

Vaughan,[1] of the University of Michigan, had shown that the Bacillus prodigiosus toxins are among the most powerful known, a fact confirmed by Tracy's[2] experiments. Further experiments with sarcoma in dogs showed that this disease would disappear under injection with the prodigiosus toxins alone, although not quite so rapidly as when combined with the erysipelas toxins. Tracy then proceeded to grow the two organisms separately and to secure a standardization of dosage by adding a certain definite quantity of the sterilized prodigiosus bouillon to each ounce of the streptococcus broth.

In March, 1895, the New York Surgical Society appointed a committee, consisting of Dr. L. A. Stimson, Dr. A. G. Gerster, and Dr. B. T. Curtis, to investigate and report on the use of erysipelas toxins in the treatment of malignant disease. At the meeting of the Society on March 25, 1896, the committee rendered the following report:[3]

"Both before and since our appointment as a committee we have been able to observe, individually and together, a considerable number of cases treated by this means, and in no case have we found any amelioration which held out a prospect of ultimate cure. We have, on the contrary, observed in some cases that the rate of growth of the disease was much more rapid during the treatment. The treatment also imposes a very severe tax upon the strength of the patient, and apparently hastens the cachexia in most cases.

"We believe that in some instances of apparent cure or marked improvement the correctness of the diagnosis is open to doubt.

"We therefore submit:

"(1) That the danger to the patient from this treatment is great.

"(2) Moreover, that the alleged successes are so few and doubtful in character that the most that can be fairly claimed for the treatment by toxins is that it may offer a very slight chance of amelioration.

"(3) That valuable time has often been lost in operable cases by postponing operation for the sake of giving the method of treatment a trial.

"(4) Finally, and most important, that if the method is to be resorted to at all it should be confined to the absolutely inoperable cases."

[1] Vaughan, Victor C.—See General Bibliography.

[2] Tracy, Martha.—See General Bibliography.

[3] "Results of Injections of Erysipelas Toxins upon Malignant Growths," *Annals of Surgery*, 1896, XLIV, 53; also, *Trans. N. Y. Surg. Soc.*, 1896.

The Surgical Society has not rescinded the decision rendered by this committee.

Moullin,[1] after an experience with ten cases, mainly sarcoma, reported his own observations and reviewed the work of others up to that time (1898). Careful study of the histories of Moullin's cases at the London Hospital reveals nothing conclusively in favor of the method.

Bashford[2] has tested Coley's fluid in mice, with no results. His conclusion with reference to it is as follows: "The fluid is not a cure for cancer, and when it cures I should take it as evidence that the patient was being treated for something which was not malignant."

Sir Frederic Eve[3] reports having used the mixed toxins in five cases of periosteal sarcoma at the London Hospital, without the slightest result on the tumor. His experience with reference to the prevention of recurrence by Coley's fluid was most disappointing. "It is undeniable," he says, "that a certain number of sarcomata disappear under, or are profoundly influenced by, the toxins, but we have no means of determining what proportion this is to the total number treated. I suspect it is only a small proportion. Although I may be forming an opinion on insufficient evidence, yet my present attitude is that I would not recommend Coley's fluid in any case of operable sarcoma, nor would I recommend it as a prophylactic agent against recurrence."

My own experience with the mixed toxins is limited to about 30 cases, in which it was used without permanent benefit. In many the treatment was attended by severe reactions and most distressing symptoms. I have not felt like advising the method, particularly in view of the fact that personal communications from 5,000 representative medical men throughout the civilized world, in response to questions concerning their experience with this agent, were, with few exceptions, unfavorable; and that, at the New York Skin and Cancer Hospital, I have seen some hundreds of advanced cases in which the mixed toxins had already been employed elsewhere without success.

Despite the adverse experience of others, Coley continues to employ his method, claiming success, as will be seen from his numerous publications.[4]

In addition to the sera above mentioned, a number of others

[1] Moullin, C. Mansell.—"The Treatment of Sarcoma and Carcinoma by Injections of Mixed Toxins," 1898.

[2] Personal communication.

[3] Eve, Sir Frederic.—"Remarks on the Treatment of Sarcoma of the Long Bones," *The Lancet,* November 16, 1912, p. 1355.

[4] Coley, William B.—See General Bibliography.

which come within the category of parasitic or bacteriological toxins have been proposed. Inasmuch as none have proved successful, space need not be sacrificed for their consideration. The literature covering the majority of these is cited in the bibliography.

B. BASED ON CYTOLYSINS OR CYTOTOXINS

VACCINES

What has been said with reference to the majority of bacterial products which are classified as sera, may be said likewise of those which come within the category of vaccines. The vaccines which continue to engage attention are those which are perhaps more commonly mentioned as residues, extracts, emulsions, or autolyzed tumor or normal tissue. They will be considered under these headings.

RESIDUES; EXTRACTS; EMULSIONS

Von Leyden and Blumenthal [1] were the first to attempt the treatment of malignant neoplasms by means of some product extracted from the tumor itself.

After experimenting successfully with the treatment of cancerous dogs by means of the serum of a rabbit that had been injected with cancer from a dog, they found it possible to cure carcinoma by inoculating the animal with juice expressed from dog carcinoma. They claimed, likewise, to have successfully treated cancer in the human subject by the injection of fluids expressed from human cancer. These results, according to von Leyden,[2] were substantiated by subsequent investigations.

According to Ewing,[3] definite cure of a growing cancer by means of vaccination "has been obtained only by von Dungern and Coca and by Gay." Many investigators have contributed to the literature of the treatment of cancer along this line, and a number of products have been suggested. The most promising of these are discussed below.

Coca-Gilman [4] *Emulsion.*—This emulsion is prepared from

1 Von Leyden and Blumenthal.—*Deut. med. Woch.*, 1902, XXVIII, 637.
2 Von Leyden.—*Zeit. für Krebsfsch.*, 1907, V, 164.
3 Ewing.—*Op. cit., N. Y. Med. Jour.*, Oct. 19, 1912.
4 Coca and Gilman.—*Philippine Jour. of Science*, IV, B, 391, 1909; also *Zeit. f. Immunitätsfsch.*, XIII, 524, 543, 1909.
See also: Von Dungern-Coca.—*Zeit. f. Immunitätsfsch.*, II, 391, 1909.
Risley, Edward H.—"The Gilman-Coca Vaccine Emulsion Treatment of Cancer," *Boston Med. and Surg. Jour.*, November 23, 1911, p. 784.
Gay, Frederick P.—*Boston Med. and Surg. Jour.*, 1909, CLXI, 211; *Jour. of Med. Research*, XX, I, 1909.

living cancer cells removed by operation. It contains the protoplasmic and nuclear elements of the cells. The method of preparation is as follows (Risley):

"The tumor removed at operation was taken under sterile precautions to the laboratory, where all surrounding connective and other extraneous tissue was cut carefully away. The tumor material was then cut into the finest possible pieces by the scissors and ground ten times in a vaccine grinder; after the first passage through the grinder an equal volume of sterile normal salt solution was added and the emulsion ground further. This made a fairly fine emulsion in which the majority, but by no means all, of the cancer cells were disintegrated. If it was certain that no contamination of the material had taken place it was immediately injected into the abdominal wall of the patient from whom the tumor was removed. About 50 c. cm. were used. The remaining portion was treated with 1 c. cm. of 5 per cent. phenol and set aside for use three weeks later. The authors soon found that their fear of transplants and toxic effects were unfounded, as neither occurred, even with the largest doses of 20 to 25 gm. of material. Sterile abscesses at the site of the inoculation were common, but did no harm."

It is impossible to review all the results of the clinical application of this method. A fairly representative expression of opinion may be found in Risley's conclusions, after employing the emulsion in a series of twenty cases:

"The conclusions arrived at, therefore, from this series are that emulsions or extracts of cancer injected into the inoperable or recently operated patient with recurrent cancer have no effect in retarding the growth or preventing recurrence, but in a great proportion of cases produce an increased activity on the part of the cancer cells, so that tumors grow with greater rapidity, and that the danger of sepsis is marked, such sepsis being in no wise beneficial to the patient or his cancer."

It is interesting to note that a study of seventy-nine cases led to the conclusion [1] that the injection of this tumor-tissue emulsion exerted no specific influence over malignant growths other than that it promptly relieved cachectic symptoms.

Vaughan,[2] *Residue.*—This is made from material from which, by special process, the non-toxic residue is extracted from the tumor.

The method is based on the work of V. C. Vaughan, who

[1] Coca, Dorrance, and Lebredo.—*Zeit. f. Immunitätsforschung, etc.*, Jena, 1912, XIII, 543-585; *Mulford Digest*, Philadelphia, 1912, I, 96-103.

[2] Vaughan, J. W.—"The Comparative Value of Different Methods of Cancer Treatment," *N. Y. Med. Jour.*, Oct. 15, 1910, p. 759; also *J. A. M. A.*, Nov. 16, 1912.

demonstrated that a cellular proteid may be split into two definite chemical parts by heating in a 2 per cent. solution of sodium hydrate in absolute alcohol. When the residue or non-toxic radical is injected into an animal, that animal becomes to a certain extent immune to the entire proteid. He has therefore used injections of cancer residue in order to render patients more or less immune to cancer. His work has been controlled by daily blood examinations of the patients under treatment, with interesting results. While the total number of white blood cells is not altered by injections, the relative proportion of the different leukocytes is affected. Following an injection of cancer residue the mononuclear cells increase within 48 hours from 5 to 40 per cent., while in the polynuclear cells a corresponding fall is seen. He draws the conclusion that a specific ferment is formed probably through a reaction with the mononuclear white blood cells.

Fichera[1] *Emulsion of Fetal Products.*—This differs from the Coca-Gilman, the Vaughan, and other extracts, residues, and emulsions in that it does not consist of cancerous material at all, but of fetal products (autolysates).

The emulsion is prepared from human embryos and fetuses of from two to six months of intra-uterine life. The fragments are placed in physiologic salt solution in the proportion of one gram to twenty centigrams. Thymol or phenol, in suitable quantity, is added, and covered by a layer of sterilized oil or toluol. The mixture is then incubated at 37 degrees C. for about two months. After carefully testing its sterility the homogeneous autolysates are then injected in doses of from 2 to 3 c. c. twice to four times a week, according to the specific gravity of the autolysates, the size of the tumor, the seat of the injections, which are made subcutaneously or directly into the tumor, and the patient's age, condition, and degree of tolerance.

Of the twenty-five patients treated by Fichera, nine showed no improvement, while in the remaining sixteen, arrest of development, retrogression, or temporary disappearance of the growth occurred.

[1] Fichera, G.—(1) "Treatment of Cancer with Autolysates of Human Fetuses," *Il Policlinico,* July 3, 1910; abstr. in the *Jour. Am. Med. Ass.,* Aug. 6, 1910, p. 545.

(2) "Gli autolizzati di tessuti nella terapia dei tumori," *Il Policlinico,* February 12, 1911, p. 197.

(3) "The Action of Products of Homogeneous Fetal Autolysis on Malignant Tumors in Man," Trans. from the Italian by Alex. R. Coldstream, *Lancet,* London, Oct. 28, 1911, p. 1194.

(4) "Tumori," Turin, 1911; abstr. in *Bull. de l'Institut Pasteur,* 1911, IX, 272.

Babcock [1] reported the use of the emulsion in twenty-one cases, with one death, apparently the result of anaphylaxis. He concludes:

"*First.*—Homogeneous emulsions or autolysates prepared from human fetuses or embryos have, in our experience, shown no distinct value in the treatment of malignant disease in man.

"*Second.*—Spontaneous or inoculated tumors of rats and mice are susceptible to various forms of treatment, and in this way differ from malignant tumors of the human family. Experimental evidence derived from tumors in the lower animals is, in many instances, misleading and valueless as applied to human practice. The favorable effects reported from novel or unusual methods of treatment for malignant disease, usually result from the enthusiasm and hope attending their introduction."

SEROUS EXUDATES AND BODY FLUIDS (SERA)

Ascitic Fluid (Hodenpyl).[2]—Of the various products of this class the one which attracted most attention was the ascitic fluid from a cancer patient.

Five years ago Hodenpyl became interested in a case of carcinoma of the breast in a woman of 37 years of age. "In spite of radical operation," says the author, "multiple recurrences appeared in the neck and in the primary scar. After the thorough removal of these, secondary growths appeared which were morphologically typical of rapidly growing carcinoma. Still other tumors developed in the neck and breast which, owing to local complications and the debilitated condition of the patient, were not removed. Later large tumors developed in the liver, which nearly filled the abdominal cavity, followed by the recurrence of excessive chyliform ascites. The prognosis was unqualifiedly bad and the patient's death seemed imminent."

The tumors in the neck and breast, however, gradually dwindled and disappeared. The abdominal tumors gradually grew smaller and became imperceptible, while the liver diminished in size and the surface became smoother.

Finally, about four years after the first operation, the liver had become approximately normal in size and position. When the report of the case was published there was no indication of

[1] Babcock, W. Wayne.—"Fetal Products in the Treatment of Carcinoma (Fichera's Method)," International Clinics, Vol. II, 23rd Series, p. 81.

[2] Hodenpyl, Eugene.—"Treatment of Carcinoma with the Body Fluids of a Recovered Case," *Medical Record,* Feb. 26, 1910.

See also: Mackay, Charles Gordon.—*Brit. Med. Jour.,* 1907, II, 138.

the original disorder other than the scars, the decreasing emaciation, and the extreme chyliform ascites, requiring frequent tappings.

This rare case of seeming recovery from extensive carcinoma, with residual chyliform ascites, suggested: (1) the theory of the formation of an antibody (often discussed) inimical to the progressive growth and persistence of the tumor cells, and (2) the alternative hypothesis that, in the process of tumor-tissue formation in the abdomen, some physical or physiological disturbance of organic or internal secretions might have occurred, leading to the accumulation or formation of substances antagonistic to tumor-cell growth or existence.

These "theoretical conceptions" were tested with ascitic fluid from this patient, first upon mice which had developed transplantation tumors, and then upon human beings suffering from carcinoma of various types. The fluid was injected in "small quantities" (amounts not stated) near or directly into the tumors, or in "large quantities" into the veins.

The general effects of these injections in man have been the nearly uniform production of temporary local redness, swelling, and tenderness about the tumors, followed by quick subsidence of these symptoms. Softening and necrosis of the tumor tissue then occur, with absorption or external discharge of the necrotic tissue, and subsequent formation of more or less connective tissue.

Forty-seven cases were reported by Hodenpyl, the greater number being distinctly unfavorable, many of them hopeless and inoperable. In all cases the tumors have grown smaller, in some they have disappeared altogether. In no instance has any tissue other than the tumor shown the least reaction after the injections, nor have any systemic effects been manifest even after large venous infusions.

The purpose of the report from which quotation has been made, was to call attention to the *"selective necrotizing* effects upon carcinoma cells of the ascitic fluid from a recovered case of carcinoma wherever, in the body of the patient, this fluid is introduced."

The records of cases and the technic of the administration of the fluid were promised at a later date. Unfortunately the untimely death of Dr. Hodenpyl occurred before any further report was made. Others have continued his work.

Some, notably Bevan,[1] have reported the unsuccessful use of the fluid.

[1] Bevan.—See General Bibliography.

Ewing,[1] in a personal report to the author, said that all cases treated by Hodenpyl died within one year. The physician's wife, who gave the serum, and who was supposed to have been cured, died of cancer soon after the death of Hodenpyl. The animals experimented upon with the serum died.

I have employed ascitic fluid from a case of malignant ovarian papillomata, according to the suggestions laid down by Hodenpyl, with six patients, but without success.

Autolyzed Cancer or Normal Tissue.—This has been employed by Pinkuss and Kloninger.[2] They describe beneficial results, but the evidence is unconvincing.

OPOTHERAPEUTIC MEASURES

Preparations of one kind or another have been made from various parts or organs of the body—blood, blood vessels (arteries), cartilage, pancreas, liver, thyroid, thymus, and placenta. None of these have been convincing, according to published reports, and they may be passed over with a partial bibliographic review.[3]

The pancreatic enzymes were thoroughly tested at the New York Skin and Cancer Hospital, as detailed in Section IX, "The Investigation of 'Cancer Cures,'" p. 242.

SUMMARY

The results described in the employment of the products of bacteria and micro-organisms in general, or in the employment

[1] Ewing, Personal Communication.

[2] Pinkuss and Kloninger.—"Zur Vaccination-therapie des Krebses," *Berl. klin. Woch.*, Oct. 20, 1913, p. 1941.

[3] Von Leyden, E., and Bergell, P.—"Ueber Pathogenese und über den spezifischen Abbau der Krebsgeschwülste," *Deut. med. Woch.*, 1907, Vol. 33, p. 913.

Bergell, P., and Lewin, C.—"Ueber Pathogenese und über den spezifischen Abbau der Krebsgeschwülste," *Zeit. f. klin. Med.*, 1907, Vol. 64, p. 185.

Gwyer, Frederick.—"Thymus Gland Treatment of Cancer," *Annals of Surg.*, July, 1907, p. 86; *New York Med. Jour.*, Feb. 19, 1910, p. 373.

Falk, E.—"Injektion von Plazentablut bei Carcinom," *Berl. klin. Woch.*, 1908, Vol. 45, p. 1394.

Woods, R. H.—"Carcinoma of the Larynx. Extirpation of primary and secondary growths; glandular recurrence; treatment with thyroid extract; disappearance of growths," *Brit. Med. Jour.*, July 1, 1911, p. 5.

Diesing.—"Die Wirkung von Schildrüsen Extract auf Magendarmkrebse," *Mediz. Klinik*, 1911, 7, p. 458.

Carnot.—"Opothérapie," Paris, 1911.

Pinkuss, A.—"Weitere Erfahrungen über serologische Diagnostik, Verlauf und Behandlung des Karzinoms," *Deut. med. Woch.*, 1912, p. 55.

of sera containing the reaction products of these organisms or their toxins, are contradictory in the extreme. Curative results have occasionally been claimed, but they are counterbalanced by what is probably a greater number of negative results, since many of the latter are not likely to have been published. The occasional apparent success is explained in some cases by errors in diagnosis. It may be surmised that when benefit has occurred it has been an accidental coincidence, and, perhaps very rarely, has coincided with a natural tendency for a tumor to disappear.

The fact that bacteriological results have been forsaken in the newer endeavor to find something derived from tumor cells, either living or killed in various ways, or from normal tissue, is sufficient evidence that confidence has now been lost in the employment of bacteriological products pure and simple. Those who have had the widest experience with the immunity reactions to cancer, as these have been studied and revealed in animals in the laboratory, have notably abstained from making any claims that the procedures they describe have any therapeutic value. This in itself should suffice as a warning that therapeutic endeavors made by individual and isolated workers are liable to errors which can be avoided or allowed for in the larger centers of research. In the present state of knowledge it is of course to be expected that further therapeutic efforts will continue to be made by individuals working along these lines, and thus we may expect to see almost every fresh advance in the laboratory directed to therapeutic ends, however unjustifiable they may be.

In regard to bacteriology and biotherapy in general we are at the present time witnessing but a repetition of what has gone on throughout all the ages in the search for a remedy for cancer. This fact should not lead to the conclusion that these efforts are not honest. But despite the sincerity of purpose which has actuated investigation, the results which have been reported are unreliable, and will continue to be so until more is learned concerning the biology of the tumor cell, and until its relation to the individual whose life it is destroying is ascertained. In Section VI will be found a large number of new facts ascertained in the laboratory which throw out of account, as empirical, most, if not all, of the claims yet made to cure cancer by biotherapy.

SECTION XI

SURGICAL TREATMENT

CHAPTER I

GENERAL TECHNIC OF SURGERY AS APPLIED TO CANCER

Year after year, in lectures, papers, and other contributions, we have reviewed certain phases of the cancer problem, endeavoring always to emphasize the fact that from remote antiquity to the present moment the only method of treatment which has stood the test of time is *surgical removal of the diseased tissue.* It must be emphasized, however, that the surgery of to-day is not the surgery of antiquity—that it is scarce fifty years old, and that, as applied to cancer, it is even younger.

Despite the fact that the older writers advocated thorough removal "by the roots," it is quite improbable that they had any clear-cut conception as to *why* the "roots" of cancer should be removed. In consequence of the general advance in anatomical and histological knowledge surgeons have come to understand how cancer arises in a small area, from which it spreads to other parts of the body, to comprehend the particular significance of certain principles of surgery with reference to the nature and the treatment of cancer, and to evolve the application of general surgical principles to the special requirements of the disease. These requirements are determined by the occurrence of the disease in different parts of the body. They vary, therefore, for anatomical reasons, or because of the greater or less risk of dissemination from one site or organ to another.

The general principles of surgical technic are the same, of course, no matter to what conditions they may be applied. There are, however, certain *special principles* which apply with enhanced emphasis to surgery as employed in the treatment of malignant disease. Failure to observe these is apt to be fraught with disappointment to the surgeon and disaster to the patient. They may be considered categorically as follows:

(1) *Thorough sterilization* of every instrument—knife, retractor, or needle—used upon the skin in an operation for cancer of the skin should be assured before it is used for any other purpose. As the operation proceeds the same instrument should not be used twice, so great is the risk of auto-infection.

We may or may not accept the theory of the contagiousness or infectiousness of cancer from one person to another, but it is undoubtedly true, as experiment and observation have completely demonstrated, that the disease is easily transferable from one portion of a cancerous subject's body to another portion. According to experiments made by the Imperial Cancer Research Fund, auto-transplantation in mice succeeds in practically 100 per cent. of cases, although errors of technic may cause it to fall to 90 per cent., whereas transplantation from one individual to another (homologous transplantation) may not succeed once in five hundred trials, although the condition is most favorable and the technic perfect.

If this be true, continuing the dissection with the knife with which the skin incision over a malignant tumor has been made, may lead to the dissemination of the cancer cells into the surrounding healthy tissue.

(2) *The danger of auto-infection* must be obviated by the careful preservation of nature's barriers. In other words, a malignant tumor must not be *cut into*. In non-malignant tumors and other operative dissections there need be no sacrifice of healthy tissue. With malignant tumors, or those suspected of malignancy, in which nature's barriers are intact, a quarter to a half inch of healthy tissue, according to location, should be removed, if possible, along with the growth. This obviates the danger of liberating cancer cells into contiguous blood and lymph channels, or into the surrounding healthy tissues.

According to the experimental researches of Paine and Nicholson,[1] should all outlying processes of cancer have been successfully removed, and one or more fragments have been left loose in the wound, such fragments will be under less favorable conditions than those of the tumor left in organic connection. Their growth will be retarded until they have become connected with the surrounding tissues and have become vascularized. Many such cells, being perhaps already of advanced cell-age, coming, as they are apt to do, from the center rather than from the actively growing periphery of the neoplasm, may die before this vascularization takes place. The survivors, however, will eventually, though more slowly, form definite recurrences.

[1] Paine, Alexander, and Nicholson, G. W.—"Surgical Interference in Cancer," *Brit. Med. Jour.*, July 22, 1911.

This is one of the explanations of the difference in the time and virulence of recurrence after operation for early cancer. It emphasizes with great force the call for the careful avoidance of the breaking down of nature's barriers.

Some surgeons advocate cutting into tumors for diagnostic purposes, following this at once by the operation or by the cauterization of the surfaces in order to obviate cell implantation or dissemination. This is permissible as a preliminary procedure for procuring sections for immediate microscopic examination when it is proposed to proceed to more extensive operation if found necessary. It necessitates extreme care and thoroughness; otherwise it entails an added risk.

(3) *Clean-cut incisions,* and as little tearing and pulling upon the tissues as possible, should be the invariable rule.

(4) *Complete removal of early accessible cancer* is always to be practiced, unless the early involvement is sufficiently extensive to entail elaborate surgical interference, when extreme age, debility, or concurrent disease which is contraindicative to surgical procedure, must be taken into consideration.

Paine and Nicholson [1] reported a series of interesting experimental studies with reference to metastasis following surgical interference in cancer. Their observations showed conclusively that the incomplete removal of a carcinoma is often followed by rapid recurrence of a greater virulence than that of the original tumor, and that this increase in the virulence is mainly due to the remaining fragments having a rich blood supply. This larger blood supply, in their opinion, is permanent, and increases as the cancer cells proliferate. When fragments of cancer tissue are left *in situ,* with the blood supply intact, even though the main vessels going to the tumor are properly ligated, those which supply the remaining fragment will promptly dilate, a collateral circulation will be established, and the original amount of blood available for its nutrition will increase.

(5) *Arterial ligation,* for purposes other than the immediate control of hemorrhage, may be mentioned in this connection. The special method of starvation ligation with lymphatic block is described elsewhere (see Chapter II, p. 383).

(6) *Operation in line with the fascial planes* has been found advantageous. This is in accordance with the theory of Handley, who holds that cancer spreads by parietal dissemination along the lymph and blood channels and the fascial planes.

[1] *Loc. cit.*

The entire subject of the spread of cancer in the individual is discussed elsewhere (see Section XI, Chapter II), and need not be reiterated in this connection. It is important, however, to bear in mind, while operating, the different avenues of extension, and to plan and execute the surgical procedure accordingly. More fascia and connective tissue should be removed than skin, even in the excision of small growths. Failure to observe this point of technic doubtless accounts for many recurrences. (*Vide infra,* paragraph 21.)

(7) *All wounds in surgery should be so placed as to prevent future irritation by the scar.* This is applicable to general surgery as a preventive precaution, in accordance with the theory of the etiological significance of chronic irritation in the production of cancer. It is of even greater importance in surgery as applied to cancer, the subject being already predisposed to recurrence, and hence more susceptible to the influence of irritation. A flap over the patella, for example, should be round or curved, in line with natural folds and wrinkles of the skin, instead of straight across; and in the neck the incision should be in line with natural creases.

In removing a non-ulcerated tumor from the breast, the incision should be made along the lower margin of the gland. The cosmetic effect is thus far better than when the skin over the breast is incised.

(8) *All manipulations of a tumor and of cancer-bearing tissue should be made with a care even greater than in other surgical procedures,* in order to prevent the accidental milking out of cancer cells into surrounding healthy tissue or into severed lymph and blood channels. Local recurrence and metastatic development may undoubtedly be fostered by failure to observe this point in the technic of surgery as applied to cancer.

In this connection Tyzzer [1] has made some interesting and valuable observations upon waltzing mice, which he summarized as follows:

"Operations incomplete but involving the incision of implanted tumors do not increase the incidence of metastases, but these grow more rapidly as the result either of an increase in the amount of food material made available by the removal of a large mass of tumor tissue elsewhere (athrepsia) or of the elimination of the element of cachexia and improvement of the physical condition which almost invariably occurs.

"Radical operations involving the removal of all the tumor—except minute masses which subsequently come into evidence

[1] Tyzzer, E. E.—"Factors in the Production and Growth of Tumor Metastases," *Jour. of Medical Research* (N. S. 23), Vol. 28, 1913, p. 309.

along the path of the inoculating trocar—if performed just prior to the period in which metastasis commenced, result in a temporary freedom from this complication, even though recurrence commonly occurs.

"Metastasis may be artificially produced by the manipulation and massage of the implanted tumor. This is accomplished as readily during the early development of the tumor as in the period in which metastasis naturally occurs.

"The production of metastases is dependent on certain demonstrable factors—the biological character of the tumor, the duration of its growth, the size of the primary mass, possibly peculiar conditions furnished by the host tissues, and, under artificial conditions, forcible manipulation.

"The so-called 'pre-metastatic period' is better accounted for by an absence of the conditions necessary for the dissemination of tumor cells than by a phase of 'active resistance' during which the further development of tumor emboli is prevented. By the early artificial dissemination of tumor cells by the manipulation of the primary tumor, this period may be greatly shortened."

The results of these investigations, according to Tyzzer, find practical application in the management of tumor patients. He says: "They are of such character that every physician should realize the irreparable harm which may result from the manipulation of malignant tumors in their early development. Although the present observations are made on a tumor with which dissemination usually takes place by way of the blood stream, it seems reasonable to expect similar results with human tumors which become disseminated by way of the lymphatics. The course of procedure to which the patient is frequently subjected, as I have repeatedly observed—the palpation of the mass in question in repeated physical examinations, the violent scrubbing often employed in preparing the field of operation—is almost identical with that which I have employed for the experimental production of metastases. It would be of advantage to the patient if each questionable tumor of the breast, for example, could be regarded as a high explosive, the least manipulation of which should be absolutely avoided both prior to and during the operation. It is not improbable that by this means metastasis and extension beyond the field of operation could be prevented and the percentages of cases cured by operation increased. From the point of view of metastasis it would appear from these results much less serious to cut into a tumor than to exert pressure upon it, although the effect of the distribution of tumor tissue throughout an extensive operation is quite naturally understood. It is not improbable that the removal of a tumor of large size from which metastasis has already occurred results in a more rapid growth of the secondary deposits. This should not weigh too heavily, however, in considering palliative operations of this sort, for internal tumors not being under the direct observation of the patient furnish a less constant source of apprehension, and the removal of a large external tumor may make the case much easier for the physician to manage."

(9) *Lymph glands and vessels contiguous to the diseased area should be removed, en masse,* if possible.

(10) *Lymph glands more remotely situated,* as in the supraclavicular region or in the axilla, in breast cancer, should be removed, if possible, *before the primary tumor is excised.*

(11) *Dissection of lymphatic or other structures should be made toward, not away from, the tumor.* It is a grave error of surgical technic, not uncommonly committed, to remove a non-ulcerated cancerous breast, for example, by a sweeping circular incision, and then to work out from this area, up into the clavicular region, out into the axilla, and down over the thorax, with a distinct possibility of the infection of the area from which the tumor has just been removed. The procedure should be reversed—the glands and all outlying tissues to be removed should be excised first, before the tumor is touched. In this way the probability of auto-infection is markedly lessened, and hence the danger of local recurrence and remote metastasis is decreased.

(12) *Raw surfaces in ulcerated cancer* should receive proper care before and during operation. When the skin over the cancer is ulcerated the danger of pyogenic infection during the operation is very great. This may be largely avoided by preliminary care of the raw surface. A few days of antiseptic treatment will often be sufficient to make a fetid ulcer fairly clean. At times of operation the local use of strong nitric acid, or actual cautery, is of advantage. Some surgeons ablate the ulcer and neighboring tissue immediately before the operation, as the safest method.

(13) *Severed lymph vessels should not be left open, but should be twisted off* in order to prevent further lymphatic permeation, after lymph glands and vessels have been removed as far as it is possible to go. The possibility of irritation by this method is no greater than by closing the vessels by means of ligatures, and is not so prolonged. Furthermore, the twisting is more quickly and more easily accomplished than the ligation.

(14) *Subsequent irritation of the tissues to be left in situ* should be prevented in every way possible by special precautions during operation. (*Vide infra,* 15, 16, 17, 18, and 19.)

(15) *Hot towels* should be used as extensively as possible *to control capillary oozing and bleeding from small vessels,* thus largely obviating the crushing or bruising of tissues by the use of clamps. Some operators leave the clamps on the vessels for a long time, with the shank pressing against the soft tissues. The use of one hundred and fifty clamps in the course of an operation means the maceration of two handsful of tissue, and the leaving of this devitalized organic material in the wound.

(16) *When it is necessary to ligate vessels* the question of subsequent irritation must be borne in mind. Instead of heavy, non-absorbable ligature material, *fine catgut dipped in physiological salt solution, or fine linen paraffined,* will control the vascularity, insuring at the same time a softer and more pliable foreign body in the tissues, thus giving rise to less irritation. Through the skin paraffined silk or linen will prove effectual in controlling capillary oozing, and will be practically non-irritating. The knot should lie between the point of puncture and the line of incision.

(17) *Drainage tubes,* which are prolific sources of irritation, *should be used as little as possible.* If the wound cannot be closed, rubber tissue may often be substituted for drainage tubes. When tubes are employed they should be made of rubber and placed where they are least apt to cause irritation.

(18) *Tension upon the wound is always to be avoided,* but particularly so in cancer subjects, because of subsequent irritation in the scar. In placing retention stitches care must be taken not to exert undue pull at any point.

(19) *A pad of uninjured fat should always be left,* if possible, to prevent the skin from lying over hard, unyielding, or bony surfaces. Fat serves as nature's buffer, and prevents future irritation and discomfort; it may also help to ward off recurrence.

(20) *The primary tumor, the lymphatic vessels and glands, and the intervening tissues should be removed, as a rule, at one operation.* It is sometimes advantageous, as in cancer of the tongue or buccal cavity, where it is impossible to work in a sterile field, to remove the glands at a subsequent operation. Auto-infection can be more definitely prevented in this way. Often, in cases where the mucous membrane is involved, one must deal, not only with the tumor, but with mixed infection. If the mucous membrane of the mouth receive infection first,

in some of these cases the glands of the neck may be more easily and safely removed later. On the other hand, if the glands are well defined, and if there is no evidence of mixed infection, it is better to go low down, for example, in the neck first, and work up, operating in the mouth later.

(21) *The extent of the skin incision* involves an important point in cancer surgery concerning which there is still divergence of opinion. Some, with Halsted, prefer to remove the skin in breast cancer, closing even extensive wounds by means of skin-grafts. Others agree with Watson-Cheyne, who rarely removes enough skin to necessitate grafting. The fact that Cheyne's statistics show a smaller percentage of skin recurrences than do Halsted's is doubtless due to the fact that the former makes a more thorough dissection of the fascia. Rodman considers any breast operation incomplete in which the fascia is not removed down to and including several inches of the rectus sheath.

(22) *Strong antiseptic solutions should not be used* in cancerous wounds, because of the danger of irritation and inflammation, with the possibility of undue contraction of the wound.

(23) In general surgery it is important to keep the hand as much as possible out of the wound. In cancer surgery it is equally important, at times, *to put the hand, gloved or ungloved, into the wound,* for the purpose of carefully examining the tissues for possible nodules of cancer which cannot be detected by the eye. Care must always be exercised, in making such examination, not to manipulate the tissues roughly, thus causing undue injury or adding to the danger of cancer-cell dissemination.

(24) *Small knots of ligatures may resemble, in feeling, minute cancerous nodules.* The extent of the disease is better determined before the ligation of the vessels is done.

(25) In sponging a wound the rule of general surgery which calls for *the patting rather than the rubbing of the surfaces* is doubly important in cancer masses.

(26) *Tourniquets should be avoided* in the surgery of cancer because of the danger of massaging cancer cells into the blood current. There is no danger of their dissemination in this way above the point of application, but there is danger of forcing such cells out into the surrounding tissues, and into the blood and lymph vessels below. This does not apply, of course, in amputations.

(27) *Scar tissue should be reduced to a minimum* over the site where cancer is most apt to manifest itself in local recurrence.

(28) *Absolute approximation of the edges of the wound* is important. If this cannot be done, leave open that part which is farthest removed from the point at which local recurrence is most apt to appear, or make an incision at a short distance, sliding the tissues over so as to close the original wound.

(29) *If it is necessary to leave a part of the wound to granulate this should not be covered with gauze,* which is harsh and stiff, but with *old, soft linen,* or with *narrow strips of rubber tissue,* which easily takes the configuration of the surface covered, and thus protects from mechanical irritation.

(30) *The granulation area, if large, should be kept soft* by means of ointment. A useful agent is one-half of one per cent. zinc oxid ointment in lanolin.

(31) *Preliminary cathetarization of the ureters,* the catheters being left *in situ,* may be important in cancer of the uterus. Some claim (1) that it renders their isolation less difficult and more quickly accomplished; (2) that it aids in the control of hemorrhage; (3) and that it lessens the liability to injury of the ureter, or to its ligation by mistake, in the Bainbridge method of arterial ligation with lymphatic block. I have rarely found preliminary catheterization necessary. It adds to the technic and increases the dangers. If employed it must be remembered that: (a) extreme care should be used not to unnecessarily manipulate the ureters either before or after removal of the catheters; (b) usually there is a purulent vaginal discharge, and the danger of bladder infection must be carefully guarded against; (c) if any difficulty is encountered in the passage of the catheter it must be withdrawn at once; (d) in advanced cancer the ureters are sometimes pressed upon by inflammatory adhesions, or their course may be somewhat altered; (e) the irritation caused by leaving the catheters *in situ* will, in the presence of cystitis, tend to carry infection into the kidneys.

PURPOSES OF THE SURGICAL TREATMENT OF CANCER

Surgery, in its application to malignant disease, aims at the following definite ends, according to the circumstances of the case:

(1) *Prevention,* through the removal of benign growths and other tissue formations which, under certain conditions, predispose to the development of cancer. (See Section VIII.)

(2) *Diagnosis.* Surgery may be brought into requisition for diagnostic purposes under the following circumstances:

(a) In the precancerous conditions discussed in Section VII.

(b) When the clinical symptoms have not begun to manifest themselves, except by tumor-formation—a mere painless lump—as in the early stages of cancer in almost any locality.

(c) When the clinical symptoms are not sufficiently well marked to warrant radical surgical intervention, or where the patient refuses it.

(d) In certain obscure abdominal conditions in which exploratory laparotomy is necessary in order to establish a diagnosis. (See Section VII, Chapter III.)

(3) *Early and Complete Removal—Cure.*—So much experimental and clinical evidence has been adduced within the past decade to prove the purely local origin of cancer that it seems hardly necessary to refer to the matter in this connection. It may be said, however, that there are still some members of the profession who speak and write, particularly to laymen, upon the subject of cancer as a general disease with local manifestations. It is not to be forgotten, furthermore, that cancer comes under the head of "Diseases of Diathetic Origin," in the *Index Medicus,* that valuable periodical catalogue of medical literature which emanates from the Library of the Surgeon General's Office.

But by those in touch with recent scientific investigation it is no longer believed that in cancer the system is permeated by something of which the manifest cancer is but an "outcrop" like the mushroom from the mycelium underground. The process is in reality exactly the reverse. The commonly accepted opinion is that, whatever may be the essential cause of cancer, the disease begins as a purely local and entirely removable, hence curable, pathological manifestation, the dissemination spreading from the primary area. There are doubtless underlying systemic conditions favoring malignancy, but essentially it seems to be a local process. Surgery, therefore, in its application to the treatment of cancer in this stage, must be performed with reference (1) to the general condition of the patient; (2) to the possibility of thorough and complete removal; (3) to the prevention of recurrence.

In view of the fact, that in the earlier or so-called removable stages of cancer, failure to completely eradicate the diseased tissue means inevitable recurrence sooner or later; and further of the fact that even removable cancer sometimes calls for very extensive dissections in order to prevent recurrence, the condition of the patient, as well as his wishes or those of his relatives, must be taken into consideration. If there are no contraindicative conditions such, for example, as extreme age, debility, or serious heart and kidney lesions, and if the patient prefers the surgical and functional risks to possible recurrence of cancer and ultimate death from the disease, no other course should receive consideration. Ruthless sacrifice of nerve and muscle, or other tissue, is certainly to be condemned, particularly unnecessary mutilation, and impairment or destruction of function. Just how far to go in the removal of cancer or cancer-bearing tissue is a question of the utmost importance. Even the most experienced operator cannot always recognize that fine line of distinction between diseased and normal tissue, ability to judge of which constitutes the imponderable, unteachable element of diagnostic skill that comes only with long and careful observation.

(4) *Removal of advanced cancer, making possible the application of special methods of treatment.*

(5) *Treatment of irremovable and incurable cancer,* making possible the application of special methods of treatment and the relief of special symptoms. (See Section XII.)

SUMMARY

The classical principles of operative technic are as applicable to cancer as to any other disease requiring surgical intervention. When the application of the special principles outlined above becomes universal among surgeons who operate upon patients with cancer there will follow a marked reduction in the proportion of cases in which recurrence takes place, and in the number of cases in which the disease terminates in death.

CHAPTER II

SPECIAL TECHNIC

No attempt is made in this volume to cover the general subject of surgical technic as applied to cancer. There are, however, certain modifications of technic, and numerous special procedures, applicable chiefly to irremovable cancer, which may be appropriately considered in this chapter. Operations which are fully described in the text-books on general surgery are not given in detail.

Various factors determine the modification or the evolution of the given surgical procedure. In some instances the purpose is the correction, as nearly as may be possible, of defects caused by the ravages of the disease or by the radical removal thereof. Illustrations of this may be found in the various plastic operations, such as rhinoplasty, cheiloplasty, and skin-grafting. In another class of operations the technic is modified in accordance with some particular theory concerning the origin or spread of cancer. An illustration of this is found in the modified breast and rectal operations in line with Handley's "permeation theory" of cancer dissemination. In others the operation is entirely palliative in its purpose, being designed to relieve pain, to control hemorrhage, to correct obstruction, or to alleviate other symptoms which result from advanced cancer. Examples of this class of procedures may be found, among others, in arterial ligation, lymphangioplasty, and neurectomy.

A. SURGICAL TECHNIC BASED UPON THE "PERMEATION THEORY" OF CANCER DISSEMINATION

Handley, with whose name the permeation theory of the dissemination of cancer is usually associated, has said:[1] "To some of my colleagues the very word 'theory' may suggest a

[1] Handley, W. Sampson.—"Recent Advances in the Surgical Treatment of Some Forms of Cancer," *The Universal Medical Record*, 1912, V, pp. 385-406.

repellent remoteness from practical affairs, to others it may connote merely a fabric of cerebral cobwebs." "The majority," he continues, "while quite willing to consider the views placed before them, will at once, and quite rightly, ask: 'What are the new facts upon which this theory is based, and what is its practical importance to me in my surgical work?'"

In answering these questions Handley has demonstrated satisfactorily to many that his theory has a strictly practical bearing upon surgical technic as applied to cancer, particularly to cancer of the breast.

For the benefit of those who are not familiar with it, a brief review of the permeation theory is given, together with the work which led up to it.

In 1889, Heidenhain[1] published his well-known researches on breast cancer, which were based upon the most careful and thorough examination of thirteen excised breasts, by means of many thousands of microscopic sections. Heidenhain thus summarizes the result of his researches:

"(1) The pectoral fascia is extraordinarily thin, and its limits, especially in stout women, are very ill-defined. So that it cannot be dissected away from the muscle without leaving behind fragments of it, unless one actually removes the surface of the muscle.

"(2) In thin women the substance of the breast, and in stouter ones at least some lobules of it, are intimately connected with the fascia and so with the muscle, so that in amputation not carried through the muscle, portions of the gland are easily left behind.

"(3) A breast in which cancer nodules are present is diseased very widely and perhaps in its whole extent. The epithelial cells of the acini proliferate, and simultaneously the periacinous connective tissues increase in amount. In the lymph vessels of the breast, along considerable stretches, epithelial cells are embolized (Langhans).

"(4) In the retro-mammary fat, lymph vessels run from the gland to the fascia, usually in company with blood vessels. In two-thirds of cases of breast cancer numerous little cancerous metastases are found in these lymph vessels. The epithelial growth advances along these preformed channels, even through thick layers of fat, quickly to the fascia.

"(5) The pectoralis major is generally unattacked so long as the carcinoma is freely movable over it. It first becomes diseased when a metastatic nodule on the fascia, growing inde-

[1] Heidenhain, D. L.—"Ueber die Ursacher der lokaler Krebsrecidive nach Amputation Mammæ," *Langenbeck's Archiv,* 1889.

pendently, advances into it, or when the primary tumor infects it by its growth in continuity. Probably in the muscle also cancer spreads first by the lymph channels and from these insinuates itself between the muscle fibers.

"(6) It is probable that during contraction of the muscle epithelial cells are distributed through the muscle with the lymph stream. Thus a muscle attacked by cancer must be suspected in its whole extent."

In the final section of his paper Heidenhain remarks:

"Accurate and systematic studies on the channels of spread of cancer in secondarily affected organs (skin, fat, muscles, bones, etc.) might be of extraordinary value. My own observations upon the spread of breast-cancer in the pectoral muscle show in what way I consider such researches would be practically valuable. But enough of speculations! It is sufficient to have called attention to this entirely unknown region."

In 1899 Stiles,[1] of Edinburgh, from the examination of over one hundred breasts removed by operation, modified and extended the conclusions of Heidenhain. Stiles insisted on the removal of the whole breast to its remotest periphery, not because he shared Heidenhain's view that any mammary epithelium left would be likely to become cancerous, but because only thus could the whole lymphatic system of the breast be extirpated. Recurrence, in Stiles' view, is likely to occur in overlooked portions of breast tissue "from cancerous emboli lurking in the lymphatics" of the unexcised portion of the breast, and in two cases he showed this view to be correct. He recognized that such cancerous emboli might be found beyond the limits of

[1] Stiles, Harold Jalland.—"On the Dissemination of Cancer of the Breast," *Brit. Med. Jour.*, 1899, Vol. I, p. 1452.

See also:

Stiles: "The Surgical Anatomy of the Breast and Axillary Lymphatic Glands considered with reference to the morbid anatomy and treatment of carcinoma: with a note on the 'nitric acid method' of demonstration," *Trans. Med. Chir. Soc. Edinb.*, 1891-2, n. s. XI, 37-70, 2 pl.; *Edinburgh Med. Journal*, 1892-3, XXXVIII, 26.

"Carcinoma of the Mamma," *Brit. Med. Jour.*, 1892, II, 673.

The Royal College of Surgeons of England, at a quarterly meeting of the Council on April 9, 1896, awarded the Walker Prize to Stiles for work done within the five years ending on December 31, 1895. According to the *Lancet*, April 18, 1896, "the work done by Mr. Stiles appeared to be most noteworthy of the prize, on the ground that he had investigated most minutely the morbid anatomy of cancer, its mode of spread, its relation to the organ in which it originates, and its relation to the lymphatic system of the part. His work on the pathological anatomy of the female breast and its accessory portions appears to be especially valuable from the fact that it has been able to demonstrate, by his nitric acid method, that the mammary acini have a much wider distribution than has hitherto been described. The importance of this in the determination of the extent of operative procedure is, of course, very great."

the breast. "The principle, therefore, which should underlie all operations for carcinoma of the mamma is the removal, not only of the breast, but also of as much of the surrounding tissue as is likely to contain the lymphatics along which cancer cells may be disseminated."

Stiles next discussed spread along the lymphatics, and figured "paravascular lymphatics distended by cancer cells." He goes on to say: "Having gained the lymph vessels, a few cells may at any time be transplanted by the lymph stream to a lymphatic gland, or may be arrested by emboli at any point along the lymph channel which leads to the lymphatic gland."

Although Stiles demonstrated that the paralobular, paraductal, interlobular, and paravascular lymphatics may be injected as it were by cancer cells, he did not appreciate the significance of his observations with respect to the general theory of dissemination. He says: "It must not be supposed, however, that in carcinomatous mammæ the lymphatics throughout the gland are extensively and continuously filled with cancer cells; in some breasts . . . emboli are numerous; in others sections from many parts of the gland have to be examined before any emboli can be discovered; in others again careful search fails to find them."

It was apparently on account of these difficulties that Stiles remained an advocate of the embolic theory of dissemination. The detection of the process of perilymphatic fibrosis by Handley supplied the explanation of these anomalous facts.

With regard to the spread of cancer in the extramammary structures, Stiles believed that by his nitric acid method he could demonstrate the spread of cancer in the skin. He also demonstrated cancerous paravascular lymphatics in the connective tissue septa joining the skin to the mamma. He next referred to the frequency of invasion of the lymphatics of the pectoral fascia, and insisted on the necessity for removing a large area of this fascia.

Stiles concluded his paper—a most valuable and original one—by a very full and accurate study of the invasion of the axillary glands in breast cancer.

Watson-Cheyne, basing his operative practice upon the conclusions of Stiles, brought about a great improvement in the results of the operative treatment of breast cancer in England. His operation differed from that of Halsted in that he widened the skin flaps extensively and removed a large area of the deep fascia.

Until 1909 all the investigations on breast cancer had been performed upon the excised breast. The embolic theory remained the only one stated in the text-books as accounting for the dissemination of breast cancer, and the observations of Heidenhain and Stiles on the spread of growth by continuity along the lymphatics appeared even to these observers to have no relation to the question of systemic dissemination, important as they were with regard to the question of local spread.

Professor Depage,[1] of Brussels, reviewing the subject of breast cancer before the International Society of Surgery, in 1908, stated truly that the embolic theory of cancerous dissemination had never been demonstrated, and that it had held its ground partly by its attractiveness as an idea, and partly because it had no serious rival. It is particularly to be remarked that neither Heidenhain nor Stiles made any attempt to dispute the truth of the theory. With regard to dissemination generally, attention remained focused upon the route which leads by way of the trunk lymphatics to the axillary and supraclavicular glands, and so to the blood stream.

It was noticed by Handley,[2] in a post-mortem examination which he happened to attend in 1909, that the abdomen was full of secondary deposits, while the chest was entirely free. Investigating the subject in post-mortem records, he found this not infrequently the case, a fact which appeared to him inconsistent with the usually accepted embolic theory. He carried out a careful investigation of the tissues in the epigastric angle, in cases of this kind, and found that the disease was obtaining direct access to the abdomen through the linea alba just below the ensiform cartilage. He then cut a longitudinal section of the tissues of the abdominal wall down as far as the umbilicus, and found that for some distance below the ensiform cartilage the lymphatics on the interior surface of the rectus sheath were choked up with cancer cells for some little distance, while lower down the tissues were free from growth. It seemed, therefore, that the disease was spreading in a centrifugal manner away from its point of origin by growing along the lymphatics much as a ringworm or a tertiary syphilid spreads.

He tested this hypothesis in other cases by cutting sections of the parietal tissues, many inches long, radiating in various directions from the primary tumor, and thus demonstrated the occurrence of what he called "the microscopic growing edge of permeated lymphatics," a zone of permeated lymphatics a few millimeters wide forming a ring of larger diameter in the

[1] Depage.—*II Congrès de la Société Internationale de Chir.*, Brussels, 1908.

[2] Handley, W. Sampson.—"Epigastric Invasion of the Abdomen in Breast Cancer." This essay was awarded in 1904 the triennial Astley Cooper Prize of £500.

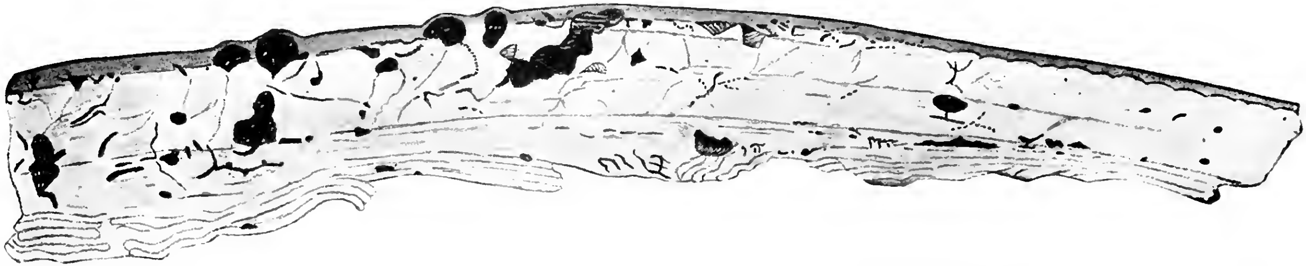

PLATE XXXVIII.—Drawing, natural size, of a translucent strip of the skin and underlying tissues taken in a radial direction from the mass of growth in the situation of the inguinal glands, to demonstrate the centrifugal spread of permeation. Note that the growth extends much further along the deep fascia than along the skin or in the muscle.

A, skin; B, subcutaneous fat, separated by the deep fascia from G, a thin layer of muscle. (Handley, in Archives of the Middlesex Hospital, Vol. VII, Fifth Report from the Cancer Research Laboratories, 1906, pp. 52–74.)

apparently healthy tissues of the deep fascia, and remaining centered upon the point at which the primary growth originated. The difficulty remained that at points inside this ring, between it and the massive primary growth, no permeated lymphatics could be found, although scattered naked-eye nodules were present. Handley inferred that the permeated lymphatics, after a time, underwent destruction, and he was able to trace, microscopically, every stage of the process by which this was accomplished, thus for the first time demonstrating the occurrence in cancer of normal curative processes. (Plate XXXVIII.) In connection with the microscopic growing edge he made a further observation that the normal cell excites no inflammatory reaction in the tissues, and that, as he expressed it, it is accepted by the tissues as a normal denizen of the body. Continuing his studies further, he showed that invasion by cancer of the internal organs of the body is very frequently brought about by the penetration of the cancer cells to the serous cavities, and their dissemination from these cavities by gravity and by visceral movements.

The application of microscopic methods on a macroscopic scale, as employed by Handley, cannot be made by a single observer to a large number of cases, since the investigation of one case occupies weeks or months.

In order to generalize the conclusions arrived at, Handley studied the post-mortem records of a large number of cases. From an analysis of these records he was able to show that the distribution of the metastases was inconsistent with the embolic theory, while it was exactly such as would be required by the permeation theory.

It is impossible to summarize his argument in a brief space, but as an example it might be cited that neither subcutaneous nodules nor bone deposits are found distal to the knee or to the elbow, that subcutaneous nodules commence close to the primary growth and spread from it in a continuously larger circle which may involve the upper arms and the root of the thighs, and that, broadly speaking, the nearer a bone is situated to the seat of the primary disease, the more likely is it to show secondary deposits.

It may also be noted that, as might be expected on the permeation theory basis, pleural adhesion delays the course of thoracic dissemination, a fact which is inexplicable on the embolic hypothesis.

Charles H. Mayo has stated that "The more recent investigations, particularly those of Handley of the Middlesex Hospital, have served to accentuate and extend Heidenhain's views." It might be more accurate to say that, while Heidenhain and Stiles first detected the growth of cancer along lymphatic vessels (a process named by Handley "permeation"), they formed no general conception of the process of dissemination other than that of the current embolic theory. By conceiving the permeation theory of dissemination, and establishing its general laws upon a firm basis of observation, Handley seems to have placed the entire surgical treatment of cancer upon a more scientific foundation.

MODIFIED OPERATION FOR CANCER OF THE BREAST

In 1912 Handley [1] made the following statement with reference to the technic modified in accordance with the permeation theory:

"It is yet too early to estimate the practical benefits of the modified operation based upon the permeation theory, which I have practiced during the past five years. I am, however, able to state that it reduces local recurrence in the skin and subcutaneous tissues to a very low percentage. When recurrence does take place, it usually happens (*a*) in the anterior mediastinal glands, appearing deeply at the anterior ends of the upper intercostal spaces, or (*b*) in the supraclavicular glands, or (*c*) in the internal organs. In all these situations it is fair to assume that cancer cells were present at the time of the original operation. My experience indicates the necessity of removing the supraclavicular glands whether they are enlarged or not, and of giving a prophylactic course of X-rays after the operation."

In some cases there is such profound shock in breast amputations that it becomes necessary to curtail the operative procedure, omitting that which is least essential.

In the view that removal of the rectus sheath is very important, I agree with Rodman,[2] especially where dissemination is extensive or where the disease is in the lower part of the breast. It is especially important in the right side, where there are avenues of extension into the abdomen along the falciform ligament.

If the glands are extensively involved in the supraclavicular region, extension has very probably taken place in the thorax, and a permanent cure cannot be expected. It must be borne in mind, however, that so far as pressure symptoms are concerned

[1] Handley.—*Op. cit.* "Recent Advances in the Surgical Treatment of Some Forms of Cancer," *The Universal Medical Record,* 1912, V, pp. 385-406.
[2] Rodman.—See General Bibliography.

internal cancer is far less distressing than is external cancer, and removal of the mass in the neck will give great relief.

The method I now employ is that of Rodman, based upon the principles of the Halsted operation with Handley's modifications, according to the permeation theory. In typical cases the skin incision extends to the anterior fold of the axilla, and is so arranged as not to enter the axilla. The skin flaps are thrown back, the costal portion of the pectoralis major is severed near the humerus. The cut end is sewed with small catgut to prevent oozing. The muscles are then laid back upon the chest and the highest glands are dissected away from the structures above. The pectoralis minor, which is rarely diseased, is denuded of all fascia. If not diseased a small strip of the pectoralis major may be advantageously left. If any of the muscle tissue is diseased, or its covering is adherent to the growth, the entire muscle must be removed. The structures are dissected from the body toward the breast. After all the fascia is separated above, I go down below and dissect a flap on the abdomen, in order to close off that line of extension. This flap of connective tissue and fat is thrown up toward the breast with the anterior layer of the rectus sheath on the same side. If the disease is low down, I frequently extend the dissection to the other side, carefully taking away connective tissue and fascia lying between the two recti muscles high up near the ensiform cartilage. The next incision is made around the breast, and the skin thrown back until it reaches over to the opposite side, and well to the posterior axillary line. The muscle, fascia, fat, and that portion of skin over the breast with the mamma, is cut away *en masse*. The large vessels entering the mediastinum are carefully drawn out, cut short, and clamped.

Care is always taken to avoid undue manipulation of the breast, in order to obviate the danger of extension.

If the hemostasis is thorough the wound may be closed without drainage, as recommended by Rodman. A small rubber tissue drain may be inserted for a day or two.

Usually there is enough skin to cover the area without grafting. It is easy to bring the skin over because the flaps are laid back so far in order to remove the fascia.

By employing the Rodman incision, with the general principles of Halsted, and recommendations of Handley, much better results should be obtained than heretofore.

My experience has been at variance with the recent statement of Murphy,[1] of Chicago, to the effect that he had never

[1] Murphy, J. B.—Clinical Congress of Surgeons of North America, 1913.

seen a recurrence in the clavicular portion of the pectoralis major or minor. However, it seems wise and safe to leave the pectoralis minor, and in some cases the clavicular portion of the pectoralis major, thus protecting the essential structure from pressure by skin and scar tissue in the axilla as Murphy has urged.

PERMEATION THEORY APPLICABLE TO OTHER LOCALITIES

According to Handley, the permeation theory of the spread of cancer probably applies to every form of carcinoma, and the technic of the surgical treatment of the disease in other localities is as much amenable to adaptation in accordance with this theory as it is in the management of cancer of the breast. He has demonstrated permeation in carcinoma of the stomach and rectum, and Lenthal Cheatle has observed it in cancer of the tongue.

At the time that Handley was working out the permeation theory with reference to the breast, I made it a practice, not only to take away all the glands, but the fascial planes and all connective tissue around the vessels and muscles in juxtaposition to the cancer. A case in point,[1] first reported in 1905, was one of extensive carcinoma of the tongue and neck. The operation was performed in two stages. On the first occasion (March 11, 1904) the submaxillary and sublingual glands on either side were removed and the salivary ducts were extirpated clear into the mouth. Many cancerous glands were removed from the region of the tonsil on the left side to the dome of the pleura, and on the right side from the tonsil to the division of the carotid artery. The mouth was then forced open and part of the large cauliflower mass on the tongue cut down with Paquelin cautery. The cauterized surface was coated daily with Whitehead's shellac. Seventeen days later a second operation was performed, when the left corner of the mouth was incised as far back as the edge of the masseter muscle, the tongue was drawn out and completely removed by an elliptical incision on the floor of the mouth encircling the tongue in front on each side. A flap of mucous membrane and muscle from the right glosso-epiglottic fold was used in making a bridge of tissue across the fauces in front of the epiglottis. The wound in the floor of the mouth was closed by chromicized catgut and

[1] Bainbridge, William Seaman.—"A Case of Extensive Carcinoma of Tongue and Neck, Presenting Points of Special Interest," *American Medicine,* March 25, 1905, Vol. IX, No. 12, pp. 477-478.

covered with shellac. The wound in the cheek was closed in the usual way and shellac applied. For ten years the patient lived a useful life, succumbing, at the end of that time, to pneumonia. At the time of his death cancer had developed along the alveolar border of the lower jaw, where he had a decayed tooth, and in the scar in the floor of the mouth. There was no recurrence in the neck.

Since this experience I have noticed that recurrence is less frequent when a large amount of fascia is removed. For a number of years I have emphasized the importance of removing far more fascia than skin. This has been impressed upon my mind many times by having observed small palpable nodules of recurrent cancer under the skin.

"OPERABILITY" OF CANCER OF RECTUM EXTENDED BY PERMEATION THEORY

Miles,[1] of Edinburgh, calls attention to the wide difference of opinion with reference to the operability of cancer of the rectum, giving the following percentages: Boas, 19 per cent.; Witzel, 25 per cent.; Czerny, 71 per cent.; Bergman, 80 per cent.; Elsberg, 65 per cent., Harrison Cripps, 25 per cent. According to his own experience, 75 per cent. of cases are operable if the radical abdomino-perineal operation is employed. If excision by the perineal methods is resorted to, over 90 per cent. will recur, and these cases he considers inoperable.

Miles cites three cases which, to his mind, prove conclusively that the operability of cancer of the rectum depends, or should depend, not, as held by many, upon the limited extent and mobility of the growth, "but rather upon the absence of visible permeation or metastatic deposits in the tissues comprising the zone of upward spread, a condition which can only be determined by abdominal exploration."

The radical abdomino-perineal operation which Miles[2] employs has given in his experience the following results:

Of 42 cases operated upon—22 males and 20 females—17 died from the operation (40 per cent. mortality). Of the 25 who survived the operation, 4 suffered from recurrence. Of the remaining 21 cases, one died of pneumonia a year after the operation, and one committed suicide three years after operation, neither presenting evidence of recurrence. Of the 19

[1] Miles, W. Ernest.—"The Treatment of Carcinoma of the Rectum and Pelvic Colon," *Glasgow Med. Jour.*, February, 1912, Vol. LXXVII, n.s. 77, p. 81.

[2] *Ibid.—Brit. Med. Jour.*, October 1, 1910.

who survived and were alive at the time of the report, 9 had been operated upon less than 2 years, and were not taken into account. Of the other 10, 3 lived, without manifest signs of recurrence, for over 4 years; 3 for over 3 years; 2 for over 2½ years; and 2 for over 2 years.

From his experience he draws the following conclusions:

"1. That cancer of the rectum spreads both intra-murally and extra-murally.

"2. That the extra-mural spread takes place in three distinct zones.

"3. That a cancer situated in the lower part of the rectum may give rise to early metastases in the pelvic mesocolon and pelvic peritoneum.

"4. That a growth in the upper part of the rectum or in the terminal portion of the pelvic colon may give rise to spread situated in the peri-anal skin and in the ischiorectal fat.

"5. That the tissues of the three zones of spread are vulnerable to spread wherever the primary growth may be situated in the rectum.

"6. That, although perineal operations can eradicate the tissues comprising the zones of lateral and downward spread, they are quite inadequate for reaching the tissues of the zone of upward spread.

"7. That the only operative procedure which completely eradicates the tissues forming the three zones of spread is the *radical abdomino-perineal.*"

Others, notably Monsarrat and Williams,[1] do not accept the permeation theory concerning the dissemination of cancer of the rectum. Handley's theory is based upon the finding, six inches or more above the primary growth, of cancer cells containing mucin or small particles of mucus, thought by him to be degenerated cancer cells. The finding of these mucin-containing cells in the plane of tissue lying between the blind ends of Lieberkühn's follicles and the underlying muscularis mucosæ was considered by him as proof of the permeation, by the cancer, of the lymphatics in this neighborhood.

Monsarrat and Williams, on the other hand, are inclined to the belief that the presence of mucin indicates the retention by the cancer cells of their normal ability to secrete mucin, rather than that the mucin is a degeneration product of cancer.

[1] Monsarrat, K. W., and Williams, Idwal J.—*Brit. Jour. Surg.*, 1913, I, 173.

PERMEATION THEORY APPLICABLE TO MELANOTIC SARCOMA

In the case of melanotic sarcoma, Handley claims to have obtained strong microscopic evidence that the process of dissemination is primarily one of centrifugal lymphatic permeation, which, in the later stages of the disease, is changed into blood dissemination.

If the operation for melanotic sarcoma is rightly planned, Handley maintains that the prospects should not be so hopeless as is generally assumed.

The principles upon which excision should be carried out are stated by him as follows: "A circular incision should be made through the skin around the tumor at what is judged by present standards to be a safe and practicable distance. The incision, situated as a rule an inch from the edge of the tumor, should be just deep enough to expose the subcutaneous fat. If necessary, two radial lineal incisions extending from the circular incision should be made on opposite sides of the tumor so as to facilitate the elevation of the skin flaps, which forms the next step. The skin, with a thin attached layer of subcutaneous fat, is now to be separated from the deeper structures for about two inches in all directions round the skin incision. At the extreme base of the elevated skin flaps a ring incision down to the muscles surrounds and isolates the area of deep fascia and overlying deeper subcutaneous fat to be removed. The fascial area is next to be dissected centripetally from the muscles beneath to a line which corresponds with that of the circular skin incision. Finally, the whole mass with the growth at its center is removed by scooping out with a knife a circular area of the muscle immediately subjacent to the growth. The edges of the wound are to be brought together as convenience dictates."

Having demonstrated that permeation of the lymphatic plexus of the deep fascia soon takes place around injected glands, just as it does around the primary growth, Handley[1] insists that excision of the glands must be carried out on exactly the same principles as excision of the primary growth. He considers it of the greatest importance to remove the apparently healthy set of glands above the obviously enlarged ones.

[1] Handley, W. Sampson.—*Op. cit.* "Recent Advances in the Surgical Treatment of Some Forms of Cancer," *The Universal Medical Record*, 1912, V, pp. 385-406. See also:

Eve, Sir Frederic.—"A Lecture on Melanoma," *The Practitioner*, February, 1903.

Acton, H. W.—*The Middlesex Hospital Journal*, 1905.

From his confessedly limited experience with his operative procedure in cases of melanotic sarcoma, Handley concludes that this disease may be removed from the category of practically incurable diseases, and transferred to that of affections such as cancer of the breast and uterus, "where fear is more equally counterpoised by hope."

B. PLASTIC PROCEDURES

When the physical house—the human body—is aflame with the "red plague"—cancer—the surgeon is called to extinguish the flame—to eradicate the disease—just as the fireman is summoned to check the fire which consumes the house of brick, mortar, and wood. When all visible evidence of the bodily flame is destroyed, the surgeon is expected to utilize his skill in repairing the damage done by this agent or by himself in his efforts to master it, just as the carpenter or the builder is expected to repair the havoc wrought by fire, or by the fireman's efforts to control it. The fireman seeks to leave no smoldering ember hidden by wall, floor or ceiling, which may later break into a flame of destruction. So, too, the surgeon endeavors to overlook no minute point of danger which may subsequently destroy limb or life. "The minimum of destruction, with the maximum of safety," is the watchword of both.

In his efforts to eradicate, not only the macroscopic, but the microscopic, manifestations of cancer, it sometimes becomes necessary for the surgeon to remove considerable areas of tissue. The disease may thus be entirely eliminated, but at the sacrifice of extensive and disfiguring tissue defects. In such cases plastic surgery may be called into requisition, the procedure varying, of course, in accordance with the requirements of the particular part involved.

In many instances the defect may be filled in with skin-grafts, taken from the patient or from another subject, with flaps from the contiguous territory of the patient's body, or with tissue transplanted from another part.

It is possible, for example, in a beginning tumor of the breast, to save skin and nipple, and to fill in the defect made by removal of the glandular tissue, with a flap of fat from the patient's back. By sliding this forward underneath the skin, the rotundity of the breast may be maintained so that it is almost impossible to detect the slightest deformity.

In cancer of the nose, by rhinoplasty a nose may be made with a flap from the patient's arm, which is kept in position over the head until union has taken place between the flap and the tissues to which it is attached. When the flap is severed from the arm, by shaping the nostrils, a fairly good nose may be made. When only the tip is involved it may be replaced to advantage by using the end of the finger. When the septum or the nasal bones are destroyed in removing the cancer a piece of cartilage from a rib may be used to advantage.

In similar manner, by means of ophthalmoplasty, otoplasty, and cheiloplasty, defects left after operation for cancer of the eye and orbit, the external ear, and the lips, respectively, may be remedied with flaps taken from other parts of the body.

Illustrative cases of these procedures are to be found in many text-books and other contributions. I have presented many such cases from time to time,[1] and need not repeat them here.

C. PALLIATIVE MEASURES

In cases of very advanced cancer, operations having for their purpose the palliation of symptoms and the prolongation of life are applicable to practically every part of the body.

NERVOUS SYSTEM

Neurectomy.—When a malignant neoplasm presses upon nerves, causing the most excruciating pain, relief may be obtained by neurectomy. As a rule the cutting of one or more nerves directly supplying the area pressed upon will suffice. It has been suggested,[2] however, that in some cases division of the sensory roots of the spinal nerves is justifiable.

In a number of instances of cancer of the floor of the mouth I have cut the branches of the inframaxillary division of the fifth nerve, giving great relief.

Decompressive or Decompression Operations are employed for irremovable tumors of the brain. Vomiting, headache, choked disc, and other distressing symptoms of pressure may be relieved by removing a portion of the skull and a corresponding area of dura, closing the soft parts over the defect.

The site selected for decompression should be over as unimportant an area of the cortex as possible.

The technic of such operations has been variously described

[1] Bainbridge, William Seaman.—See General Bibliography.
[2] Rowntree, Cecil.—"Tumors," in "A System of Treatment," edited by A. Latham and T. Crisp English, Vol. I, p. 135.

by Macewen, Horseley, Cushing, and others. For a full list of references bearing upon the subject the reader is referred to the general bibliography.

Perforation of the corpus callosum has been suggested and employed by Anton and v. Bramman in cases of tumors of the brain accompanied by internal hydrocephalus and choked disc with threatened blindness. These authors also advocate puncture of the corpus callosum as a preliminary procedure when intracranial pressure is sufficient to interfere with palpation of the brain or removal of the tumor.

LYMPHATIC SYSTEM.

Lymphangioplasty.—Handley[1] suggested a procedure, to which he applied the term "lymphangioplasty," for the relief of brawny arm, the distressing condition which is said to complicate 16 per cent. of cases of advanced cancer of the breast. This painful swelling of the arm is accounted for by Handley as being the result of the blocking of lymph channels by the growth itself, or by the perilymphatic fibrosis which, according to the permeation theory of dissemination, accompanies the extension of mammary cancer.

The method consists in providing artificial lymphatic channels in the subcutaneous tissues of the brawny arm by the passage of long strands of silk from the wrist to the healthy tissues beyond the axilla.

Lymphangioplasty is not applicable to all cases of brawny arm. The procedure is contraindicated under the following circumstances:

(1) In the presence of pleural effusion on the affected side.

(2) When the pain is largely due to pressure of the tumor upon the brachial plexus.

(3) When the mammary growth is so extensive that a sufficient area of non-ulcerated skin is not available for carrying the threads.

(4) When infection of the silk threads is inevitable because of the generally septic condition.

(5) When the threads have to pass through cancerous tissue.

Handley has recently made the following statement[2] concerning the method:

[1] Handley, W. Sampson.—"A New Method for the Relief of the Brawny Arm of Breast Cancer and for Similar Conditions of Lymphatic Œdema," *Lancet*, March 14, 1908, p. 783; also Archives of the Middlesex Hosp., Vol. 12, p. 28.

[2] Personal communication, December 2, 1913.

"There is undoubtedly a considerable percentage of failures, and since I have not been able to find out how to distinguish cases in which success will follow and those in which the operation will be useless, I have not felt able to press the operation on patients as much as I did when my experience was smaller. I would now offer it to patients as affording a good chance of relief, but would avoid anything like a promise of relief.

"I accept provisionally Madden's statements that the silk becomes blocked by fibrosis around it within a relatively short time. If this is so, then the successful cases must be explained somewhat as follows: That the temporary drainage supplied by the silk restores the current in certain lymphatic channels of the limb which are merely temporarily occluded by the pressure of the œdema, and not actually fibrosed, and so reëstablishes the disturbed equilibrium.

"Though the operation has not fulfilled all my hopes, I believe it will have a place in surgery until some better substitute than amputation of the limb is available."

I have employed lymphangioplasty in six cases of brawny arm. In one case infection took place, despite the best of care. In two cases there was no appreciable benefit. In the three remaining cases there seemed to be great improvement and marked relief for a number of months.

The principle of lymphangioplasty has been applied by Handley and others to the continuous subcutaneous drainage of the abdomen in cases of ascites resulting from advanced cancer of the abdominal organs.

Paracentesis abdominalis, or the withdrawal of ascitic fluid by tapping, should be resorted to, as required, in all cases of hydroperitoneum or abdominal dropsy. This condition may accompany any form of malignant neoplasm, primary or secondary, of the abdominal organs. It is particularly notable in the rare variety known as malignant papillomata. The fluid reaccumulates very rapidly, necessitating frequent tappings. In one case, cited elsewhere (Section VII, Chapter III, p. 214), the patient has been tapped seventy-six times.

Thoracocentesis, or the withdrawal of pleuritic fluid by tapping, sometimes affords great relief in advanced cancer of the breast, in which the blocking of the lymph channels extends to the thoracic cavity, and in extensive cancer of the lung or mediastinum. Repeated tappings are necessary, but, when resorted to, life may be prolonged considerably, and the patient rendered much more comfortable.

VASCULAR SYSTEM

"STARVATION LIGATURE"

HISTORY

The ligation of arteries is said to have been practiced at least eighteen hundred years before Harvey discovered the circulation of the blood (1616-1619). It is not known who first employed the method, but ligation of bleeding vessels for the control of hemorrhage is mentioned in the writings of Celsus (30 B. C. to 50 A. D.), and of Galen (131-211 A. D.). Aëtius (502-575 A. D.), Avicenna (980-1037 A. D.), and others of the early authorities on surgery employed the ligature for the control of hemorrhage and in the treatment of aneurysms.

With the discovery of the circulation, and the development of knowledge concerning the part played by the blood in the nourishment of normal, as well as abnormal, tissue, the method of ligating arteries increased in scope. It then came to be applied, not only for the control of hemorrhage occurring as the result of accident or surgical procedure, and for the treatment of aneurysm, but for the purpose of causing atrophy of organs or other parts of the body, and to lessen the nutrition of inoperable new growths, thus checking their further development and perhaps causing their disappearance.

The last-named use of the ligature has given rise to the term "starvation ligature." The procedure has been applied to the uterus, ovaries, testes, spleen, thyroid gland, tongue, and other parts of the body.

The discoverer of the circulation of the blood is himself credited with originating this newer application of the ligature in surgery, although it has been said that Johan Muys, in 1626, recommended the "starvation method" by means of arterial ligatures, basing his idea upon procedures then in use among veterinarians. For a long time the method was known as "Harvey's method." His first and, so far as is known, his only application of the procedure was made in 1651, when he is said to have treated successfully a case of elephantiasis of the scrotum and testicle by ligating the spermatic artery.

The surgery of the arteries, particularly the "starvation ligature," remained a practically neglected field for many years. The next recorded application of this procedure was made by Lange in 1707, when he employed it in the treatment of goiter.

A hundred years elapsed before the method was again employed. Travers, in 1809 (or 1805, according to Tuffier), employed it in the treatment of a tumor of the orbit, said by some writers to have been a fungus growth, and by others an aneurysm. He tied the common carotid artery, this being the first recorded instance of ligation of the vessel for this purpose.

Dalrymple, in 1813, tied the same vessel in the treatment of a fungus growth of the orbit (see Mauclaire,[1] 1900, p. 365.)

Sir Astley Cooper, in 1814, tied the humeral artery in an unsuccessful attempt to starve a sarcoma of the radius.

In 1815 Maunoir treated a sarcocele of the testicle by tying the spermatic arteries.

Cancer of the tongue was treated by Mirault (1833) by the ligation of the lingual artery, and similar experiments were made by Roux, Demarquay, Broca, Magendie, and others.

Bier, in 1889, tied the hypogastric arteries for the purpose of causing atrophy of the prostate, and in 1893 the same authority treated fibro-adenoma of the breast by the ligation of the mammary arteries. Simultaneous ligation of both internal iliac arteries for prostatic hypertrophy was practiced by Willy Meyer, von Bergmann, Koenig, and others.

In 1889 Wyman treated malarial hypertrophy of the spleen, and in 1894 Tricomi treated enlargement of the spleen (leukemic splenomegaly) by ligating the splenic artery.

Sir Frederic Treves, in 1892, reported a case of sarcoma of the buttock treated by ligation through a median incision of the internal iliac artery of the affected side. The tumor was of three months' duration, and was not amenable to excision. Remarkable shrinkage of the growth followed the operation, the pain was greatly diminished, and the patient was able to walk for ten months. He died fourteen months after the operation. In reporting this case Treves emphasized his belief that sarcoma is more amenable to treatment by this method than is carcinoma.

In 1893 George Wherry reported, in the London *Lancet,* "a successful case of intraperitoneal ligation of the internal iliac artery." The method was applied in this instance to a large pulsating tumor upon the upper posterior and outer part of the left innominate bone, of nine months' duration. The tumor shrank, the pain became much less, and the pulsation ceased.

In an article on the ligation of arteries in cases of malignant disease, published in 1895, John H. Packard, of Philadelphia, reported, among others, a case of pulsating tumor of the upper part of the left femur, treated by means of ligation of the internal iliac artery of the affected side. The throbbing and pain ceased, some motion returned to the hip-joint, which had been

[1] Mauclaire.—See General Bibliography.

fixed in partial flexion by the mass of the tumor, the growth diminished in size, and, after nearly six months in the hospital, the patient, able to walk about on crutches, was discharged.

The application of the "starvation ligature" to tumors of the carotid and pelvic regions is given below, under separate headings.

LIGATION AND EXSECTION OF THE EXTERNAL CAROTID ARTERY (DAWBARN METHOD) IN THE TREATMENT OF MALIGNANT TUMORS OF HEAD AND FACE

The literature of the general subject of ligation of the carotid arteries is voluminous, and it is not my purpose to review it here. For those who are particularly interested ample references are given in the General Bibliography.

The literature of the "starvation ligature" as applied to these vessels is meager and chaotic. Neither in the earlier days of its use nor in later times has the method received the attention it would seem to merit.

In his masterful essay: "Surgical Anatomy and History of the Common, External, and Internal Carotid Arteries," Dr. John A. Wyeth, of New York, analyzes 789 cases of ligature of the common carotid, of which 87 were for malignant tumors other than those of the orbit, and 8 for malignant vascular tumors of the orbit. He also analyzed 18 cases of ligation of the internal carotid, and 91 of the external carotid. Of 67 cases of ligature of the external carotid alone, 15 were tied "to relieve or cure so-called malignant growths." Of the 18 cases in which the internal carotid was tied, in only one case was the artery alone ligated, and, according to Wyeth, "nothing reliable as to the practicability of this operation can be deduced." This one case was not one of the "starvation treatment," and we have no statistics upon the "starvation ligature" as applied to the internal carotid alone.

The case of Travers, mentioned above, re-awakened interest in this procedure as applied to the common carotid. The idea was gradually extended, a number of cases of the successful treatment of malignant tumors of the head and face being reported by this method.

Pilz, in 1868, published all the cases of ligation of the common carotid; Madelung, in 1874, published all cases of ligation of the internal carotid, and Wyeth, in 1878, brought these tables up to date, with the addition of a number of cases reported to him by correspondence. Lipps, in 1893, brought Madelung's table to date.

The first application of a ligature to the external carotid artery in the treatment of a tumor of any sort, according to Madelung and Lipps, appears to have been made about 1830. It was not until 1854 or 1855 that bilateral and unilateral ligation of this artery for malignant growths of the buccal cavity, tongue, and pharynx was employed in seven cases without success by Maisonneuve. These were reported for the first time by Guyon, in 1868.

The editor of "Schmidt's Jahrbucher," in 1875, cites the next reported case, in which Lannelongue, in 1873, is supposed to have ligated one or both (it is not stated whether the ligation was bilateral or unilateral) external carotid arteries for inoperable sarcoma of the tongue and face.

The results in all these cases are given in the tabulated records contained in Wyeth's essay, mentioned above, to which the reader is referred for more detailed information.

The next record of this procedure is found in the *Medical News,* 1887, where, among nineteen others mentioned, Dr. J. D. Bryant, of New York, reports two cases in his own practice.

Another decade passed before the "starvation ligature," as applied to the external carotid arteries, is recorded again. Tuffier, in a paper read before the French Surgical Association in 1897, cited vaguely three cases in which he tied the external carotid. He also summarizes the history of the procedure.

In 1900 Mauclaire reviewed briefly the history of *"ligatures atrophiantes."*

It was not, however, until the appearance of the Samuel D. Gross Prize Essay, "The Treatment of Certain Malignant Growths by Excision of the External Carotids," by Robert H. M. Dawbarn, that the "starvation ligature" became the modified "starvation treatment" which is now an established procedure in the treatment of advanced cancer of the mouth and face.

In this work Dawbarn says, with reference to simple ligation: "In some instances formidable and rapidly growing tumors *have* disappeared after ligation of the nutrient vessels, although there must always be some doubt, so incomplete are the records of these, as to the accuracy of the diagnosis of malignancy. It appears probably the fact that undoubted malignancy—as shown by glandular implication, cachexia, microscopical examination, etc.—has never been permanently arrested by ligature." Of the thirteen cases of ligation of the external carotid reported by others and tabulated by Dawbarn, not one, he says, was attended by a permanently favorable result, although it must be remembered that most of them were desperate cases, and that ligature was practiced as a forlorn hope rather than as the operation of choice.

Realizing that the results of this procedure were unsatisfactory because of the rapid resumption, by anastomosis, of free arterial circulation, Dawbarn sought to modify the method by effecting the starvation of the growth by means of carotid *excision.*

Since the publication of Dawbarn's essay many operators have followed his method, with varying degrees of success, some verifying the observations of the essayist.

The technic which I employ as to ligation, excision, and injection is essentially that described by Dawbarn, only such modifications being made as the exigencies of the individual case require.

TECHNIC OF CAROTID EXCISION AND INJECTION OF THE TWO TERMINAL BRANCHES

The patient is placed upon the operating table with the head well extended, the face held averted to the opposite side, and the shoulders raised by means of a pad or block.

The incision extends from near the level of the tip of the ear downward, close behind the angle of the jaw, to the level of the middle of the larynx, the greater cornu of the hyoid bone being considered the median point. This brings the ends of the incision over the artery, but between these points the cut curves inward, with the convexity toward the median line of the neck. The mid-point of the curve is thus brought 1½ centimeters nearer the median line than ordinarily advised, and gives a gain in speed and safety.

The incision made, the work proceeds from its lower toward its upper extremity.

The superior thyroid, as a rule, is the first branch of the external carotid to be exposed. It is easily recognized by its definitely downward course throughout. Tracing this back to its origin, the external carotid is reached, and a provisional ligature, to be used for quick control of hemorrhage in case of need, is placed around the vessel. The ligature, of chromicized catgut, is not tightened until later.

The superior thyroid is now tied in two places with chromicized catgut, and divided between the ligatures.

Each branch in turn, except the two terminals and, on occasion, the occipital, is treated in like manner, the ligation and division in each case being as far as practicable from the parent vessel, the object being to sacrifice as much as possible of the branch and its own unnamed branches. Sometimes, as in the case of the lingual, a sub-branch, as the *dorsalis linguæ,* may be individually ligated.

When all the branches except those mentioned have been ligated and divided, the external carotid itself is tied in two places and divided between the ligatures.

The distal end of the external carotid is now seized and carried underneath the transverse loop of the twelfth nerve, and again beneath the conjoined stylohyoid and posterior belly of the digastric, coming to the surface at a level above these two muscles.

When it is possible, the artery is followed up to its bifurcation and a ligature is placed around the apex of the V made by its terminal branches.

Especial care must be exercised here not to injure the lower branches of the *pes anserinus* and thus cause facial paralysis, nor to cut through some of the smaller ducts of the parotid gland, thus causing a salivary fistula. General care must be exercised to avoid the various nerves and vessels in the contiguous tissues. It goes without saying that the tissues throughout the operation should be handled very gently.

I prefer the special Dawbarn artery clamp to the blunt aneurysm needle for passing the ligatures.

With all other branches ligated and divided, and the main trunk treated in like manner, the operator next proceeds to inject the two terminal branches, the superficial temporal and the internal maxillary.

For this purpose the following special instruments, in addition to the equipment for ordinary surgical work, are required: (1) A metal or glass syringe that permits of sterilization, with a capacity of about 10 c. c. The nozzle should be sufficiently slender to readily enter the rubber tubing by means of which the syringe is attached to the cannula. (2) A glass cannula, 4-5 cm. in length, with a caliber of about that of an ordinary steel knitting needle. One end is beveled, the other grooved transversely for holdiing the thread by means of which the cannula is attached to the rubber tubing above mentioned. (3) A piece of rubber tubing 2-3 cm. in length. A short piece of soft-rubber catheter may be used for this purpose. (4) One pair of scissors, small, sharp-pointed, and straight. (5) One tenaculum, smallest size, single hook. (6) Glass pipette, extremely slender-nosed and long, with rubber nipple somewhat similar to a medicine dropper.

Instead of wax or other substances which have been suggested for the purpose, I have usually used melted paraffin for injection.

The melted paraffin is contained in a vessel which floats in a much larger vessel filled with sterile hot water, in which is placed a thermometer. By means of the latter the paraffin is kept at the required temperature (120° F.—49° C.). In the water of the outside vessel are also placed the syringe and cannula, which have been previously securely connected by means of the rubber tubing, all having been sterilized and filled with the melted paraffin ready for the injection.

The injection is made in the following manner: At a point as close as possible to the parotid gland, deep in the substance of which the two terminal branches are buried, the external carotid is nicked, the cannula inserted, and tied in place. Not more than 2 c. c. (30 minims) of paraffin should be injected into the carotid near to where it disappears within the parotid gland, this amount having been proved by Dawbarn's experiments upon dogs to be the safe amount.

The paraffin is not allowed to fall below 108° F., at which temperature it solidifies. By working rapidly the injection may be finished before this happens.

In order to prevent the danger of clotting in the vessels to be injected, it is well to have a duplicate syringe and cannula filled with warm normal salt solution, and to distend and flush the vessels with from 10 to 20 c. c. of the solution before proceeding to inject.

Dawbarn has demonstrated that there are twenty-nine ways by which the external carotid system may anastomose with other systems, chiefly the internal carotid, and that twenty-two of these (which are supplied by the superficial temporal, internal maxillary and occipital arteries) may be obstructed without giving rise to sloughing of normal tissue.

In certain cases, therefore, where the disease is supplied with blood by the occipital branch, this may also be injected. When this is to be done it is accomplished, before the injection of the terminal branches, in the following manner: The other branches of the external carotid having been ligated as described, and this vessel itself tied low down but not yet cut, it is now tied a second time, just distal to the occipital branch. A transverse or oblique nick is then made with the scissors in the wall of the external carotid at a point just proximal to the branching of the occipital. The cannula is inserted into this by the aid of the tenaculum, and firmly tied in place. The same amount of paraffin that is injected into the carotid, viz., 2 c. c., or 30 minims, is now injected into the occipital. When the injection of the paraffin is completed the occipital is ligated with catgut and cut through; or, if solidification of the paraffin has already taken place, the vessel may be simply divided.

In some cases I have ligated and excised the external carotid artery, according to the technic described, without injecting the terminal branches. The latter part of the technic was omitted because of the fear of additional shock. The condition of the patient must determine the omission of this part of the operation.

Possible abnormalities in the artery should always be borne in mind. The pupil on the side of the ligation should be watched when the ligature is thrown around the external carotid. Dilatation of the pupil upon compression of the vessel, before the tie is made, is indicative of an abnormality, probably the condition which exists in the dog—the absence of an external carotid artery. In such cases the mortality is much greater than in those in which the carotid is normal.

It is also to be borne in mind that there may be a displacement of the external carotid artery, and that the internal carotid may be ligated in its stead.

The procedure is repeated on the other side ten days later. Dawbarn's experience, and that of other surgeons, including my own, has abundantly proved that nothing short of this seemingly very radical procedure will permanently shut off the blood supply to the parts. Early anastomosis takes place where only ligation is done, and the injection unquestionably tends to delay for a much longer time the establishment of collateral circulation.

INDICATIONS FOR THE OPERATION

It is to be borne in mind that the method is employed only in advanced cases. In the majority of instances, therefore, it is merely palliative. In many cases the operation cannot be employed because of the great induration of the tissues, which makes it impossible to reach the artery. To cut into cancer tissue in order to ligate the external carotid renders it necessary subsequently to ligate the common carotid, which is a dangerous procedure, because, by cutting into cancerous tissue, extension of the disease is apt to be hastened.

(1) Age is no bar to the operation, it having been successfully performed in persons of ages ranging from early infancy to extreme old age. In my own experience the operation has not been done in the case of any very young individual, but in his essay Dawbarn mentions one patient, a baby six months old, upon whom a double excision was performed, and an-

other eighteen months old, also a double excision. Recovery followed in each case.

(2) The procedure is indicated in the treatment of carcinoma as well as sarcoma, although the results have proved more favorable in the latter disease. The reason may be sought in the method of extension of the two diseases. In carcinoma the lymphatic system is largely concerned, the blood vessels, as a rule, not being involved. Cutting off the blood supply, therefore, does not prevent extension, particularly upon or near the surface, through the lymphatics. In sarcoma, on the other hand, the blood vessels are mostly concerned in the extension of the process, the lymphatics rarely being involved. Retardation of growth and relief of other symptoms are sufficiently great in carcinoma, however, to warrant the employment of the method in cases where there are no contraindications.

(3) Sometimes, in operable cases, that is, where the tumor is wholly or partially removable, it may be advisable to excise both external carotids in order to avoid deformity, the patient being kept under strict surveillance for any signs of increased growth of the tumor.

(4) In operable cases, where the malignant growth is removable, but where the disease is sufficiently advanced to indicate probable early recurrence, excision of both external carotids may be resorted to with the hope of preventing recurrence. Furthermore, in such cases, this procedure, preceding the removal of the growth, insures an almost bloodless field and the possibility of a more extensive and thorough operation.

(5) In irremovable tumors of the base of the tongue, floor of mouth, and pharyngeal wall, and other inoperable cancers of the region supplied by the external carotid and its branches, the procedure may be indicated as a measure of last resort.

It may be said, in concluding the discussion of carotid excision, that the objection sometimes raised against the method, viz., possible gangrene of normal tissue, has not been substantiated in the experience of Dawbarn and of other surgeons, including my own. A sufficient blood supply remains to maintain the vitality of the parts. The coldness and pallor of the face, lips, and tongue, which are always to be noted after the operation, are not of long duration.

The other objections, (1) injury to nerves with resultant facial paralysis, and (2) a possible fatal result arising from the anomalous conditions of the arteries concerned, are overcome by a thorough knowledge of the anatomy of the parts and by careful surgical technic.

The chief objection, it seems to me, to the method as practiced by Dawbarn (ligation, excision, and injection), is the danger of shock. I have not employed this procedure in a large number of cases for this reason, preferring to utilize simple ligation. In cases which are too far advanced for the Dawbarn operation, because of the involvement of the terminal vessels, simple ligation has been employed, going below and tying the external carotid on each side, with whatever branches it is possible to reach without cutting into cancerous tissue.

The following table summarizes my experience with the full technic of ligation, excision, and injection, and with simple ligation of the external carotid artery.

TABLE I

Arterial Ligation for Irremovable Cancer in the Mouth and Throat, etc.
Report of Forty-nine Cases

SUMMARY OF RESULTS

Case No.	Length of Life After Operation.	Effect Upon Symptoms.	Effect Upon Hemorrhage.	Remarks.
1	Three Months.	Improved.	Controlled.	
2	Two Months.	Improved.	Controlled.	
3	Two Months.	Improved.	Controlled.	Lost sight of.
4	Three Months.	Improved.	Controlled.	Lost sight of.
5	Five Days.	Improved.	Controlled.	
6	Three Months.	Improved.	Controlled.	Lost sight of.
7	Five Months.	Improved.	Controlled.	
8	Ten Weeks.	Improved.	Controlled.	
9	Two Months.	Improved.	Controlled.	Lost sight of.
10	Two Months.	Improved.	Controlled.	
11	Five Months.	Improved.	Controlled.	
12	One Day.	Improved.	Controlled.	Died of Cerebral embolism.
13	One Month.	Improved.	Controlled.	Lost sight of.
14	Six Weeks.	Improved.	Controlled.	
15	One Month.	Improved.	Controlled.	Lost sight of.
16	Four Months.	Improved.	Controlled.	
17	Four Days.	Doubtful.	Controlled.	
18	Six Days.	Doubtful.	Controlled.	
19	Two Days.	Doubtful.	Controlled.	
20	Three Months.	Improved.	Controlled.	Lost sight of.
21	Four Months.	Improved.	Controlled.	Lost sight of.
22	Three Months.	Improved.	Controlled.	
23	Five Months.	Improved.	Controlled.	
24	Five Months.	Improved.	Controlled.	
25	Two Days.	Doubtful.	Controlled.	Died of Cerebral Apoplexy.
26	Four Months.	Improved.	Controlled.	
27	Nine Days.	Doubtful.	Controlled.	
28	Ten Months.	Improved.	Controlled.	

TABLE I—Continued.

Case No.	Length of Life After Operation.	Effect Upon Symptoms.	Effect Upon Hemorrhage.	Remarks.
29	Eleven Days.	Doubtful.	Controlled.	
30	Two Months.	Improved.	Controlled.	
31	One Month.	Improved.	Controlled.	Lost sight of.
32	One Day.	Doubtful.	Controlled.	Died of Nephritis.
33	Two Weeks.	Improved.	Controlled.	
34	Five Months.	Improved.	Controlled.	
35	Three Months.	Improved.	Controlled.	
36	Six Weeks.	Improved.	Controlled.	
37	Nine Weeks.	Improved.	Controlled.	
38	Four Days.	Doubtful.	Controlled.	
39	Four Days.	Doubtful.	Controlled.	
40	One Month.	Improved.	Controlled.	Died of Pneumonia.
41	Three Months.	Improved.	Controlled.	Lost sight of.
42	Seven Weeks.	Improved.	Controlled.	
43	Eight Days.	Doubtful.	Controlled.	
44	Three Months.	Improved.	Controlled.	Living March 10, 1914.
45	Seven and a half Months.	Improved.	Controlled.	Died of Pneumonia.
46	Two Months.	Improved.	Controlled.	Died.
47	Two Months.	Improved.	Controlled.	Living March 10, 1914.
48	One Month.	Improved.	Controlled.	Died.
49	One Month.	Improved.	Controlled.	Living March 10, 1914.

Summary of Results

Remarks

1. Barring twelve patients who died from one to eleven days after operation, the length of life varies from one month to ten months.
2. The effect upon symptoms was improved in thirty-nine cases; doubtful in ten cases.
3. Hemorrhage was controlled in all cases.
4. Of the forty-nine cases comprising this series, thirty-six died, ten were lost sight of, and three were living March 10, 1914.

Common carotid	7
Internal carotid	1
Internal and external carotid	1
Subclavian	1
Maxillary	1
Lingual	5
External carotid, right side	16
External carotid, left side	16
Both external carotids	1

"STARVATION LIGATURE," WITH LYMPHATIC BLOCK, IN THE TREATMENT OF ADVANCED CANCER OF THE PELVIC ORGANS

HISTORY[1]

The application of the "starvation ligature" to the pelvic organs was first recorded by Fritsch, who, in 1885, advised and practiced ligation of the uterine arteries in a case of fibroma of the uterus. He was followed by Hofmeir, Antal, Dorsett, and a number of others.

To Baumgartner seems to belong the credit for having first tied the uterine arteries in a case of inoperable cancer of the uterus, report of which was published in 1888. The arteries were ligated by way of the vagina when this was possible, or were merely divided and clamped. When the vaginal route was impracticable he ligated the internal iliacs at the origin of the uterine arteries. A number of surgeons followed him in this procedure.

Kelly, in 1893, was the first to ligate the internal iliac arteries in the treatment of cancer of the uterus, the procedure in this case being one of emergency to control unexpected and otherwise uncontrollable hemorrhage. In the course of abdominal hysterectomy for squamous-celled carcinoma of the cervix with extension to both broad ligaments, the ligature cut through and free hemorrhage ensued. Both internal iliacs were ligated, the hemorrhage was controlled, and the operation completed. The patient's condition was such, however, that it was impossible to remove all the diseased tissue. When readmitted to the hospital six months later, to be treated for a vesico-vaginal fistula, careful examination failed to reveal the slightest evidence of the carcinoma. The patient died ten months after the operation. The method was employed by Kelly and his assistants in other cases, but they seem to have abandoned it entirely during the last few years.

One of the most enthusiastic advocates of the "starvation ligature" in the treatment of advanced cancer of the uterus was the late Dr. William R. Pryor, of New York. In 1896 he ligated the internal iliacs with the avowed purpose, not only of controlling hemorrhage, but for the "starvation of tissue which cannot safely be removed."

Pryor ligated, through a median abdominal incision, the ovarian, the internal iliac, and the obturator arteries. He simultaneously ligated both internal iliacs in thirty-four cases

[1] See General Bibliography.

of malignant disease of the uterus, with one fatality. In his experience life was much prolonged and suffering diminished.

It may be recalled in this connection that Pryor advocated ligation of the internal iliac and ovarian arteries of each side, not for purposes of cure, but as a palliative measure. He considered it an excellent means of securing temporary relief for ineradicable cancer of the uterus. In his Essay mentioned above, Dawbarn quotes Pryor, in this connection, as claiming nothing more than this for the method. "He has had no real cures, no permanent cessations of malignant development, and knows of none at the hands of others."

From 1897 to 1900, Hartmann and Fredet carried on a series of anatomical investigations and published a series of articles on the subject of ligatures applied for the purpose under discussion, and in 1898, before the Paris Surgical Society, they presented a series of specimens obtained from patients who had been operated upon for cancer. They concluded that for purposes of hemostasis ligation of the uterine artery is superior to that of the internal iliac. They were of the opinion that the course of the malignant tumor is not apparently modified by the ligation. The results noted were temporary diminution of hemorrhages and offensive discharges.

Tuffier, at the Paris Surgical Congress in 1897, advocated the "starvation ligature" in the treatment of inoperable malignant growths of the uterus. This was followed by a succession of published observations by Roux, Morestin, Jonnesco, Hanow, and others.

Pozzi, in his treatise on gynecology, mentioned the starvation ligatures merely to condemn them, while many others, both in Europe and America, in discussing the treatment of irremovable cancer of the uterus (generally designated "inoperable"), mentioned the subject in the most casual manner or neglected it entirely.

In 1904 Rouville, in collaboration with Martin, published a series of cases in which the starvation method was employed, with absolutely no effect upon the development of cancer of the uterus. It was considered, however, a good palliative measure.

In 1905 Zykow, a Russian surgeon, published a summary of five cases in which he employed complex or multiple ligatures, with resulting retardation of growth, amelioration of the usual symptoms, and improvement of the general condition.

The subject was next brought to notice by P. Cantier, who, in 1907, reviewed the history of the "starvation ligature," summarized many of the published cases, and formulated his own conclusions. This contribution was called forth by one of de Rouville's cases, in which the uterine arteries were ligated, with resulting control of hemorrhage, but progressive development of the neoplasm.

In 1908, at the Annual Clinical Lecture on Malignant Disease, at the New York Skin and Cancer Hospital,[1] I presented several patients and cited the histories of others (Cases I, II, III, IV, and V of the appended table), operated upon for irremovable pelvic cancer, according to the earlier method which I had employed in these cases.

From the various cases reported there may be deduced quite enough evidence of a favorable nature to warrant a wider application of the method in the treatment of irremovable cancer of the pelvic viscera than is now being made. Jonnesco, for example, reports eight cases of inoperable cancer in which he employed complex ligatures, with the result of arrest of hemorrhages and discharge, spontaneous elimination of the neoplastic products, and improvement of the patient's general condition for six and ten months. (*Congrès International de 1900, Paris.*)

My experience, extending through seven years, leads me to conclude that arterial ligation for irremovable cancer of the pelvic organs, to be effective either in controlling hemorrhage or in checking the malignant growth, must be employed with reference to the possibilities for free anastomosis to the vessels supplying these organs. The vessels cannot, as in the case of the external carotid, be subjected to any more procedure than ligation in two places and division between the ligatures, and consequently it is necessary to ligate as many of the vessels as possible without causing death of normal tissue. My experience, therefore, is not in keeping with that of Fredet, who, as already noted, believed ligation of the uterine arteries to be more effective in controlling hemorrhage than ligation of the iliac trunks. On the contrary, ligation of the uterine arteries alone is not always sufficient to control hemorrhage or check the growth of the neoplasm, nor is ligation of the utero-ovarian arteries sufficient in all cases, a fair blood supply to the parts being maintained through anastomosis of other branches of the internal iliac, or possibly through the establishment of a recurrent circulation.

Ligation of the internal iliac artery of each side close to the bifurcation of the common iliac, thus shutting off all the branches of the posterior and anterior trunks of the first-named artery, eliminates the chief blood supply of the uterus, vagina, and pelvic fascia. If they are accessible without cutting into

[1] Bainbridge.—See General Bibliography.

cancerous tissue, and if it is deemed necessary or advisable, the procedure may be made more thorough by ligating individually the obturator, superior vesical, or other branches of the internal iliac, in addition to the main ligature of this vessel.

The deep epigastric and its branches, from the external iliac; the ovarian, which arises from the abdominal aorta; and the sacra media, which arises from the abdominal aorta and partly supplies the lower lumbar and sacral region, including the posterior surface of the rectum and mesorectum, furnish further possibilities of anastomosis. If, in addition to the internal iliacs, the ovarians and the sacra media are ligated, the blood supply is sufficiently lessened to control immediate or possible subsequent hemorrhage, and to offer a reasonable hope of checking the growth of the neoplasm.

From the above it will be seen that failure in many instances may have been attributable to the fact that the ligation was not sufficiently extensive to control the blood supply to the pelvic organs, thus proving ineffective in either of the purposes for which it is mainly applied. I have personally found this to be the case, and accordingly have gradually extended the method. In the communication mentioned above, under the head of "Tying off vessels in the pelvis," the following statement is made: "The ovarian and uterine arteries, or, if the uterine cannot be reached, its nearest branches, may be tied off; or the anterior division of the internal iliac artery may be ligated on the side of the most extensive disease, the uterine and ovarian of the opposite side being ligated at the same time."

While this procedure was advantageous, as shown in the histories of two cases reported in the article mentioned (Cases I and III of the appended table), the amplified technic now employed is of greater promise because it allows the freer application of other methods of treatment, surgical or non-surgical, and still further lessens the danger of hemorrhage, while increasing the possibility of checking the extension of the malignant process. In suitable cases both internal iliacs just below the bifurcation of the common iliac, both ovarians, and the sacra media are now ligated. In some instances it is necessary to ligate the common iliac just above the bifurcation, as in Cases VII and XIV.

THE PURPOSES OF THE METHOD

I. *To Control Hemorrhage.*—(1) As an immediate life-saving measure; (2) to render possible necessary surgical measures; (3) to insure the patient against the possibility of death from hemorrhage during the progress of irremovable cancer.

In many instances the alarming hemorrhage is the first symptom which causes the patient to consult the surgeon. Life is not infrequently in immediate danger, and in such cases, even where little else can be done surgically, life may be prolonged and mental and physical suffering mitigated by ligating the arteries as indicated. In cancer of the cervix, where curettage for removal of necrotic débris is indicated, the procedure may cost the life of the patient from hemorrhage, unless the curettage is preceded by ligation. An illustration of this occurred some time ago in the New York Skin and Cancer Hospital. One patient refused laparotomy. She was curetted and everything done for her that was possible under the circumstances, but she died in the hospital some weeks later from hemorrhage which could not be controlled by styptics and packing. Another patient (Case XL), who occupied a bed in the same ward at the same time, submitted to laparotomy, the vessels were ligated, after which curettage was done. The patient gained flesh and strength, left the hospital in due time, and lived many months. Another illustrative instance is Case VIII of the appended table.

II. *To Check Extension of Malignant Growth.*—The assumption that a malignant process may be checked by cutting off the blood supply to the affected part seems to have been amply demonstrated by the recorded cases, although, as noted above, it must be admitted that there is a wide divergence of opinion on the subject. In some instances, where, because of the circumscribed nature of the growth, the possibilities of a more complete cutting off of the blood supply were greater, as in the cases reported by Packard, Treves, Wherry, and others, cure seemed to follow the procedure.

This naturally leads to the conclusion that, if in advanced cases there is any real retardation of the process, even though it be temporary, then, in cases not so far advanced, where the method may be applied without injury of any kind, the possibilities for permanent arrest of growth warrant a wider application of the starvation treatment than has yet been made.

The method was employed in cases herewith reported solely as a palliative measure, yet it is fair to assume that the extension of the process was checked to some extent, as judged from the improvement in the patients' general condition, the lessening of fetor and other symptoms of advanced cancer of the pelvic organs.

III. *To Mitigate Physical Pain and Mental Suffering.*—

In many cases the pressure resulting from the growth gives rise to intense suffering, which is relieved or greatly lessened by the shrinkage which follows the ligation of the nutrient vessels to the diseased parts. This shrinkage is sometimes noted by those witnessing the operation. As soon as the vessels are ligated the parts are seen to pale and perceptibly diminish in size. Attention has already been called to the relief of other pressure or constriction symptoms, made possible by the control of the blood supply, as in breaking up non-cancerous adhesions, freeing the ureter, etc.

IV. *To Diminish Absorption of Poisonous Products.*—The sepsis which is characteristic of advanced cancer is not always from the cancer of the uterus, but from the broken-down glands in the pelvis. The method not only facilitates the removal of glands between the uterus and the receptaculum chyli, but it in a measure shuts off the *lymphatic* avenues of absorption. Cachexia is thus lessened, and the patient is rendered more amenable to measures which tend to promote elimination. This paves the way for general tonic treatment, which is of little or no avail when the system is thoroughly clogged and poisoned by the absorption of toxic products.

V. *To Facilitate the Discharge of Pus and Necrotic Tissue.*—It is of the utmost importance that a free outlet for pus and necrotic tissue be maintained. In some cases this is impossible without danger of fatal or exhaustive hemorrhage, and consequently it is no common thing to find acetone or other styptic or cauterant agents applied to the cervix, so constricting the outlet that the pus and necrotic débris are dammed up in the uterine cavity. Sometimes, by inserting the finger into the os and pressing upon the fundus, a gush of pus follows. With the vessels securely ligated, the uterus may be curetted away to a shell, allowing free exit to discharges without fear of hemorrhage. Once thoroughly cleared, the discharge grows less, and naturally the fetor is diminished.

VI. *To Permit the Application of Other Surgical and Non-surgical Measures.*—Curettage; cauterization by the Byrne method; the application of thermic coagulation or thermoradiotherapy; the employment of ionic surgery, according to the method of Betton-Massey; the intelligent and systematic use of acetone and other caustics; the use of radium and radiogelatin, if desired; the trial of the various non-surgical methods of treatment which from time to time are proposed; and the institution of the necessary hygienic and dietetic régime, are all facilitated by preliminary ligation of the arteries, as described. Furthermore, a great deal more can sometimes be accomplished surgically than seemed feasible before the abdomen was opened. It is even possible, in some cases, to extirpate the uterus where this seemed entirely out of the question before laparotomy. Volvulus and other abnormal conditions of the intestines, causing obstruction or other symptoms, may be discovered and corrected upon opening the abdomen for purposes of ligation. Cases IX, XIII, and XIV, of the appended table are illustrations of this.

In many cases the patient is dying not so much from the cancer *per se* as from the absorption of toxic products, some of which do not emanate from the cancer. In the effort to relieve suffering, morphin is often given in enormous doses. As a consequence there is a veritable locking up within the body of poisons which now, even more than under other circumstances, need to be eliminated. Furthermore, in the effort to keep up the vitality, large quantities of milk are given, which it is often difficult for the patient to assimilate or eliminate. Thus, well-meant attempts to aid are in reality merely hastening the end. How much better, then, in suitable cases, to ligate the vessels as described, thus obviating the danger of hemorrhage, while opening up the avenues for the escape of poisons, and fitting the patient for receiving the fullest benefits from whatever medicinal, dietetic, or hygienic measures may be employed.

OBJECTIONS WHICH MAY BE RAISED TO THE PROCEDURE

(1) That it is impossible to get at the vessels without extensively entering cancerous tissues. If this were really true in all cases, naturally the operation would have no place of usefulness in surgery for cancer, for, as I have already said, it is imperative not to cut into cancerous tissue and thus disseminate cancer cells. But it is rarely true. In many instances extensive adhesions are the result of old inflammatory processes having nothing whatever to do with the cancer, and probably of prior existence to it.

(2) That enlarged glands around the bifurcation of the common iliac may be encountered and cut into. Unless such glands are broken down, which is very uncommon, it is possible to dissect them out. In Case II of the table the disease had so softened the bifurcation of the common iliac on the right side that it would have been only a very short time until the vessel would have given way and death from hemorrhage or profound sepsis would have ensued.

(3) That it is impossible to reach and ligate the arteries

without harm to the ureters. Such an objection is void when the operation is performed by one whose skill is sufficient to warrant undertaking the operation at all. The ureters are easily identified and injury to them readily avoided.

(4) That gangrene may follow cutting off the blood supply, particularly that terrible sloughing may follow in cases where the bladder and rectum are involved. Of course it is understood that complete and absolute deprivation of blood to any part means its death *en masse*. This does not apply in the method here described, inasmuch as an ample blood supply is left for the maintenance of vitality. The objection with reference to the bladder and rectum is discussed in the next section.

INDICATIONS

It is not to be inferred that arterial ligation with lymphatic block is advocated in all cases of advanced cancer which are no longer amenable to the usual surgical methods for the removal of cancer of the pelvic organs. It may be advised under the following circumstances:

(1) When hemorrhage, which threatens death, cannot be controlled by other measures.

(2) When hemorrhage has been sufficiently severe or frequent to warrant fear of fatal return at any time.

(3) When hemorrhage is sufficient to cause a constant drain on the patient's vitality.

(4) When the disease is so extensive as to render curettage dangerous because of hemorrhage.

(5) When there is reason to believe that, by controlling, to a certain extent, the progress of the disease, the pain, fetor, and discharge may be lessened.

(6) When it is possible, by this means, to relieve various pressure symptoms.

(7) When, in the presence of advanced cancer of the pelvic organs, other conditions which may not be directly due to the cancer call for exploratory laparotomy.

(8) When, in cases seemingly too far advanced for total extirpation with hope of permanent cure, there is yet a possibility that life may be prolonged and suffering relieved, and in some cases a radical cure effected. Case 26 is an illustration of this condition.

(9) When all other measures have failed to give any relief from the symptoms in the given case, when the patient demands that something more be done, and when there is any hope of mitigating suffering or prolonging life.

TECHNIC

The steps of the operation may be given categorically, as they apply to the average case:

(1) *Laparotomy.*—The abdomen is opened by an incision made a little to the right or left of the median line, the cut being carried quickly through all the tissues, except the rectus, which is drawn to one side, down to the peritoneum. The abdominal cavity having been opened, the patient is placed in the Trendelenburg position. The intestines are displaced toward the diaphragm, in order to give free access to the pelvis, being dyked off with warm pads.

(2) *Ligation of Ovarian Arteries, with Double Oöphorectomy.*—The ovarian arteries are ligated just above the brim of the pelvis, one place being sufficient. Pagenstecher thread or strong silk is used for this purpose. The upper part of the broad ligament close to the uterus, with the Fallopian tube, is tied off as well. The ovary, tube, and upper part of the broad ligament, including the parovarian tissue, are exsected.

(3) *Incision of Peritoneum on Posterior Wall of Abdomen.*—This is accomplished by a curved incision extending from one internal iliac artery to the other, with the convexity upward, and prolonged downward along the top of the broad ligament, already divided in the preceding step of the operation. As a rule this gives free access to all the retroperitoneal structures in the pelvis.

(4) *Ligation of Internal Iliac Arteries.*—The internal iliac artery of each side is ligated in turn. The artery is carefully separated from its vein and ligated in two places. The first ligature is placed just below the bifurcation of the common iliac, and the second, half an inch below the first. With a large, plain clamp the artery is crushed between the two ligatures.

(5) *Ligation of the Common Iliac Artery.*—One may be forced, unexpectedly, to ligate the common iliac artery. An advanced atheromatous condition of the vessel, with beginning erosion due to softening of the glands at the bifurcation, may render it necessary to ligate the common iliac just above this point in order to obviate the danger of rupture. This procedure, of course, is to be resorted to only in such unforseen emergencies. In cases 12 and 24 the common iliac of the right and left sides, respectively, was ligated just above the bifurcation, with no unfavorable symptoms in either case.

(6) *Ligation of the Uterine Arteries.*—If it can be ac-

complished without cutting into cancerous tissue, the uterine arteries may be ligated.

(7) *Ligation of the Obturator.*—What has been said with reference to the uterines applies likewise to the obturator.

(8) *Ligation of the Sacra Media.*—If large enough to warrant it, the sacra media is next ligated. One ligature is sufficient for this.

(9) *Lymphatic Block.*—Either before or after this ligation operation, the glands along the iliacs are removed *en masse,* if possible, from the receptaculum chyli to the obturator foramen. The glands situated within and around the obturator foramen are removed. I have without difficulty removed the glands in this locality, taking them out *en masse* and placing a hot pad over the area. If any of the glands are so softened that there is danger of breaking them and soiling the peritoneum, the operator must choose between the two evils—leaving them to break down early of themselves, or taking them out and running the risk of rupturing them, thus soiling the peritoneum. The danger of this contamination is slight if one is careful to pad off the rest of the peritoneum, and to carefully approximate the edges of the peritoneal wound, covering over the raw surfaces.

(10) *Correction of Accompanying Pathological Conditions.*—After completion of the ligation and removal of the lymph structures, all accompanying pathological conditions are corrected as far as possible and in proper sequence. A great deal more can sometimes be accomplished surgically than seemed possible before opening the abdomen. The uterus may be extirpated in some cases where such a procedure seemed impossible before laparotomy. Volvulus, "kinks," and other abdominal conditions of the intestine, causing obstructive and other symptoms, may be discovered and corrected upon opening the abdomen for purposes of ligation. In many cases the victim of cancer may suffer coincidentally with non-malignant disease of the ovaries and tubes. Removal of these diseased structures may relieve the symptoms, the patient having cancer but not as yet suffering directly from it. There is no reason why a woman should be handicapped by displacement or disease of the ovaries and tubes just because she is the victim of cancer. She should be relieved if possible of these conditions despite the cancer. The ovaries, therefore, should be removed. This is done for the following reasons: (1) In accordance with Beatson's theory of the presumptive influence of ovarian irritation upon the cancer process. (2) An otherwise normal ovary may be subjected to a degenerative process as a result

of pressure irritation by the cancer, or by adhesions later in the course of the disease, giving rise to additional preventable discomfort. (3) By cutting away the upper part of the broad ligament, in the removal of the ovary, a certain amount of collateral circulation is shut off, thus facilitating the lessening of the blood supply to the cancer.

(11) *Closure of the Abdominal Wall.*—The posterior layer of peritoneum is closed, the intestines and omentum are replaced in position, and the anterior layer of peritoneum is brought together with a few simple stitches. For purposes of expedition the abdominal wall is then often closed *en masse* with through-and-through sutures of silkworm gut or silk thread.

(12) *Curettage.*—After the abdomen is closed the patient is placed in the lithotomy position and thorough curettage, by the Byrne or other method, may be resorted to when circumstances warrant. With the arteries ligated as above described, the uterus may be curetted to a shell without danger of hemorrhage. Zinc chlorid or acetone may be applied to the interior of the uterine cavity, or, if feasible, thermocoagulation may be employed.[1] Curettage and the adjuvant measures mentioned may be employed immediately after the ligation operation, or a week or ten days later, by which time the tissues will be much more contracted. I prefer the latter.

SPECIAL POINTS OF TECHNIC TO BE OBSERVED

Success or failure in arterial ligation with lymphatic block is dependent upon various features—the extent of the disease, the patient's general state, and the complicating pathological conditions. Aside from all these, however, success is largely dependent upon certain points of technic which should be borne in mind:

(1) *Adhesions.*—If cancerous adhesions are very extensive, so that it is necessary to break them up in order to reach and ligate the vessels, the operation is contraindicated. Extensive adhesions sometimes result from old inflammations, and may have no relation to the cancer so far as their origin is concerned. Inflammatory adhesions may be safely dealt with and the vessels ligated. It is important, therefore, to differentiate between malignant and non-malignant adhesions.

[1] Bainbridge.—(1) "The de Keating-Hart Method of Fulguration and Thermoradiotherapy," *Medical Record*, July 6 and 20, 1912; (2) "Fulguration and Thermoradiography," *The Jour. of Advanced Therapeutics*, January, 1913.

See also: *The International Clinics*, September, 1913, and *The Reference Handbook of Medical Sciences*, September, 1913.

(2) *Cicatricial Contractions.*—Cicatricial contractions in the diseased tissue frequently cause pressure upon the ureter, which otherwise may not be involved in the malignant process. In such event the ureter may be stripped up without breaking the cancerous adhesions, thus relieving pressure in the neighborhood. If the ureter is directly involved in the cancer this does not apply. Separation of the ureter is accomplished by inserting the finger or a blunt instrument between it and the connective tissue which lies over the cancerous tissue, and carefully working the ureter free.

(3) *Occlusion of Ligated Artery.*—The entire success of the operation may be nullified by failure to occlude the vessels ligated. Complete closure is rendered certain by ligating in two places and crushing the artery between the two ligatures.

(4) *Hemostasis.*—Absolute hemostasis is important. Oozing from veins may be controlled with pads dipped in hot saline solution and left in place on one side while attending to the other.

(5) *Removal of Glands.*—In dealing with suspicious glands situated directly in contact with large blood vessels, one must be careful to ascertain whether they are softened underneath, while apparently normal on the surface. Failure to note such conditions may lead to rupture of an underlying or contiguous blood vessel, or to the soiling of the peritoneum by the breaking of such softened glands.

(6) *Injury to Iliac Veins.*—Care must be taken not to injure the internal iliac vein, which lies just to the mesial side and behind the artery. This is the greatest danger of the operation.

CLINICAL APPLICATION

As previously stated, the operation of arterial ligation with lymphatic block is distinctively a procedure for advanced cancer of the pelvic organs, in which the disease has progressed to such a stage that complete removal is impossible. However, if the method were employed earlier in the course of malignant development, better results would doubtless be obtained. Latterly I have had recourse to this procedure earlier than formerly, and in such cases the results have been very satisfactory. When the cancer has become disseminated, especially when it has progressed to the stage characterized by vesico-vaginal fistula, it is too late to hope for very much. In Case 43, however, a patient with vesico-vaginal fistula was alive and able to work seven months after operation. The tendency should be toward an earlier rather than a later application of the method.

Cases of advanced cancer in the wards of the New York Skin and Cancer Hospital in which ligation has been employed have been compared with others, there at the same time, in which it was not resorted to, and it has been found that in the former cases the patients are far more comfortable, and progress much more satisfactorily than in the latter.

The appended table summarizes fifty-six cases in which arterial ligation with lymphatic block was employed in advanced cancer of the pelvic organs. It is to be remembered that the majority had already undergone one or more operations, or had been told that there was no hope for them. Many were stupefied with sedative drugs, and were merely waiting for the relief which comes with death.

TABLE II.— ARTERIAL LIGATION FOR IRREMOVABLE CANCER OF PELVIC ORGANS, WITH LYMPHATIC BLOCK.*

No.	Name.	Age.	Hospital or Private.	Diagnosis: 1. Clinical. 2. Microscopic.	Date of Operation.	Condition Found Upon Laparotomy. Palliative measures other than arterial ligation with lymphatic block.	Arteries Ligated.	Effect Upon: 1. Pain. 2. Fetor. 3. Discharge. 4. Hemorrhage. (When Present.) 5. Extension. 6. General Condition.	Results.	Remarks.
1	Mrs. M. S.	30	Skin and Cancer.	1. Fibromyoma. 2. Fibromyoma, with carcinomatous degeneration.	Sept. 26, 1906.	Fundus uteri seat of several nodular fibromyomatous tumors, one the size of an orange; all apparently undergoing carcinomatous degeneration. Hysterectomy; double Oöphorectomy.	Uterines. Ovarians.	1. Pain (associated with menstruation) relieved; none other complained of. 2. None present. 3. None present. 4. None present. 5. Checked. 6. Improved.	Discharged, Oct. 18 1906. Living, March 12, 1911.	Ligation, in this case, was resorted to sufficiently early, apparently, to check any extension which may already have taken place into contiguous structures. At any rate, patient is alive and perfectly well at present time with no evidence of recurrence.
2	Mrs. F. S.	38	Skin and Cancer	1. Carcinoma uteri. 2. Carcinoma.	Apr. 15, 1907.	Uterus firmly adherent to rectum; irremovable. Left tube and ovary removed; right involved in cancerous process.	Ovarians. Broad ligaments ligated so as to include uterines, which could not be reached for ligation.	1. Mitigated. 2. None present. 3. Lessened. 4. None present. 5. Doubtful. 6. Improved.	Died, June 24, 1907.	This was a very advanced case, and while the disease was probably not checked in its extension, the patient's remaining days were certainly made more comfortable than could otherwise have been expected.
3	Mrs. F. W.	39	Skin and Cancer.	1. Carcinoma of uterus, ovaries, tubes, broad ligaments, secondary to carcinoma of rectum and vagina. 2. Carcinoma.	Feb. 7, 1908.	Extensive involvement of pelvic organs, including tubes and broad ligaments; bladder; rectum. Ovaries and tubes removed.	Ovarians. Broad ligaments near wall of pelvis constricted by ligatures.	1. Mitigated. 2. Lessened. 3. Lessened. 4. None present. 5. Apparently checked. 6. Distinctly improved.	Died, Aug. 17, 1908.	On June 25, 1907, the diseased portion of the vagina and the anterior rectal wall were exsected. Recurrence took place, with pelvic extension, and patient was placed on the enzyme treatment, Feb. 5, 1908. (No. 94 of Enzyme Report.) At last operation uterus was too extensively involved for removal. Uterine arteries could not be reached for ligation, without entering cancerous tissue. Patient left hospital in fair condition. Was able to be up and around and lived in comparative comfort, and with no hemorrhage, for six months.

*The technic, including double oöphorectomy, was performed as per description unless otherwise specified.
An inventory was taken of the cases July 1, 1913. Patients were traced wherever it was possible, and the conditions found are herewith reported.

4	Mrs. H. G.	38	Skin and Cancer.	1. Carcinoma of pelvic viscera with extension to abdominal viscera. 2. Carcinoma.	Feb. 26, 1908.	Very extensive involvement with many adhesions, some of which were cancerous; tissues very friable; disease irremovable. Intestines and parietes bathed in purulent fluid; a pool of pus found in pelvis. Posterior surface of bladder and a contiguous loop of gut gangrenous.	Ovarians. Broad ligaments tied off *en masse.*	Negative.	Died, Feb. 27, 1908.	Because of the advanced stage of the disease, this case was an unfavorable one for operative interference, but in view of the following facts it was decided to resort to ligation as a last hope of relief: (1) The increasing intensity of the pain. (2) The frequency and severity of the hemorrhages, which it was impossible to control by other means. (3) The patient's piteous plea that something be done to relieve her. A mistake was made in this instance in ligating the broad ligaments, which were involved in the cancerous process, and in breaking up some of the cancerous adhesions. The internal iliacs could not be reached for ligation. Septic peritonitis supervened, and the patient died the day following operations. (No. 33 of Enzyme Report).
5	Mrs. F. D.	49	Skin and Cancer.	1. Carcinoma of uterus and bladder. 2. Carcinoma.	Apr. 18, 1908.	Extensive involvement of uterus, broad ligaments and bladder; vesico-vaginal fistula; irremovable.	Ovarians. Uterines.	1. Markedly lessened. 2. Markedly lessened. 3. Markedly lessened 4. None present. 5. Apparently checked. 6. Greatly improved.	Died, Nov., 1909.	Patient lived many months, able to do light housework. Was present at annual clinic, in May, 1909, one year after operation. (No. 80 of Enzyme Report).
6	Mrs. M. R.	36	Skin and Cancer.	1. Carcinoma uteri. 2. Carcinoma.	Apr. 27, 1908.	Irremovable cancer of uterus and adnexa with extension to cul-de-sac of Douglas and posterior wall of bladder. Double oöphorectomy.	Ovarians. Uterines.	1. Mitigated. 2. Lessened somewhat. 3. Lessened somewhat. 4. None present. 5. Doubtful. 6. Improved.	Died, Sept. 1, 1908.	....

ARTERIAL LIGATION FOR IRREMOVABLE CANCER OF PELVIC ORGANS, WITH LYMPHATIC BLOCK.—*Continued.*

No.	Name.	Age.	Hospital or Private.	Diagnosis: 1. Clinical. 2. Microscopic.	Date of Operation.	Condition Found Upon Laparotomy. Palliative measures other than arterial ligation with lymphatic block.	Arteries Ligated.	Effect Upon: 1. Pain. 2. Fetor. 3. Discharge. 4. Hemorrhage. (When Present.) 5. Extension. 6. General Condition.	Results.	Remarks.
7	Miss M. M.	34	Skin and Cancer.	1. Carcinoma of uterus, adnexa, vagina. 2. Carcinoma.	Dec. 2, 1908.	Extensive involvement of pelvic organs, including the glands. Irremovable.	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. None present. 5. Apparently checked. 6. Improved.	Died, May 1, 1909.	Autopsy showed uterus to be small. Extension of malignant process not as great as condition at time of operation would suggest.
8	Mrs. R. L.	50	Skin and Cancer.	1. Carcinoma uteri. 2. Carcinoma.	Feb. 12, 1909.	Irremovable cancer of uterus, involving broad ligaments.	Internal Iliacs. Ovarians. Sacra Media.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Entirely controlled. 5. Apparently checked. 6. Improved.	Died, Aug., 1909.	For eight months this patient had had an almost continuous bloody discharge, with an occasional severe hemorrhage. After operation she gained in weight and strength. No more hemorrhages.
9	Mrs. E. S.	32	Skin and Cancer.	1. Carcinoma uteri. 2. Carcinoma.	Aug. 10, 1909 (by member of staff). Mar. 7, 1910 (Bainbridge).	1st Operation: Cervix entirely destroyed by malignant process; glands in region of large vessels involved. Irremovable. 2d Operation: Irremovable cancer of pelvic viscera; left internal iliac patent; right internal iliac occluded.	1st Operation: Internal Iliacs. 2d Operation: Internal Iliacs religated. Sacra Media.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Not entirely controlled by first operation; completely controlled by second. 5. Doubtful. 6. Improved.	Died. June 4, 1910.	This case illustrates the importance of tying the artery in two places, and crushing between, in order to insure its complete occlusion.

10	Mrs. F. E. M.	32	Middletown, Conn., Hospital service of Dr. John E. Loveland.	1. Carcinoma uteri. 2. Carcinoma.	Mar. 8, 1909.	Extensive involvement of uterus and contiguous structures. Irremovable.	Internal Iliacs. Ovarians. Sacra Media.	1. Distinctly lessened. 2. Distinctly lessened. 3. Distinctly lessened. 4. Completely controlled. 5. Apparently checked. 6. Markedly improved.	Died, Jan. 25, 1910.	Patient was bedridden, in a grave condition, constantly in danger of hemorrhage, and considered an inoperable, hopeless case, with only a short time to live. After operation she gradually recovered strength and was able to go out about town at will. On one occasion, after undue exercise, there was slight venous oozing from vagina, but no real hemorrhage.
11	Mrs. W. S.	50	Private.	1. Carcinoma uteri. 2. Carcinoma.	May 8, 1909.	Irremovable cancer of uterus; large ulcerating mass in pelvis. Left ureter obstructed by pressure from cancerous adhesions; ureter stripped up and pressure relieved.	Internal Iliacs. Ovarians. Sacra Media.	1. Mitigated. 2. None present. 3. Lessened. 4. Completely controlled. 5. Apparently checked. 6. Greatly improved.	Died, Oct. 2 1909.	Severe hemorrhage was the chief symptom before operation. Curettage had been attempted, but the tissues were too friable. Acetone was applied locally after curettage; radio-gelatin used after ligation operation. Patient recovered sufficiently to preside at her own table, to go to the mountains and later to the seashore, and to take automobile rides.
12	Mrs. B. W.	38	Skin and Cancer.	1. Carcinoma of abdominal viscera (secondary to carcinoma of uterus, and following hysterectomy by another surgeon). 2. Carcinoma.	May 24, 1909.	A large carcinomatous mass was found in abdomen, involving glands in iliac region. Common iliac artery was softened at bifurcation, on right side.	Internal Iliacs. Right common Iliac (just above bifurcation). Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. None present. 5. Doubtful. 6. Improved.	Discharged, June 15, 1909. Moved away, not heard from since.	Ligation of Common Iliac caused no symptoms further than temporary edema of right leg. The condition of the vessel was such that hemorrhage from its rupture could be safely predicted. Ligation effectually prevented this contingency.

ARTERIAL LIGATION FOR IRREMOVABLE CANCER OF PELVIC ORGANS, WITH LYMPHATIC BLOCK.—*Continued.*

No.	Name.	Age.	Hospital or Private.	Diagnosis: 1. Clinical. 2. Microscopic.	Date of Operation.	Condition Found Upon Laparotomy. Palliative measures other than arterial ligation with lymphatic block.	Arteries Ligated.	Effect Upon: 1. Pain. 2. Fetor. 3. Discharge. 4. Hemorrhage. (When Present.) 5. Extension. 6. General Condition.	Results.	Remarks.
13	Miss M. R.	38	Skin and Cancer.	1. Carcinoma uteri. 2. Carcinoma (very malignant)	June 7, 1909.	Extensive involvement of uterus and adjacent structures; bladder; rectum. Irremovable.	Internal Iliacs. Ovarians. Sacra Media.	1. Mitigated. 2. Distinctly lessened. 3. Distinctly lessened. 4. Completely controlled. 5. Doubtful. 6. Markedly improved.	Died, Aug., 1909.	Patient was very much weakened from hemorrhage, which had been almost continuous for several weeks. General condition, which had been very poor, was distinctly improved after operation. Disease gradually progressed to fatal issue, but there was no further hemorrhage.
14	Mrs. R. B.	53	Skin and Cancer.	1. Carcinoma uteri. 2. Carcinoma.	July 20, 1909.	Floor of pelvis extensively involved, so that removal of uterus was impossible. The vagina was so constricted by the growth and cicatrix that it was impossible to introduce a speculum.	Internal Iliacs. Ovarians.	1. Entirely relieved for several months. 2. Lessened. 3. Lessened. 4. Controlled. 5. Doubtful. 6. Improved.	Died, May, 1910.	Patient considered herself cured for a number of months. She did her housework, and refused to consider herself invalid. Finally, in March, 1910, the bladder perforated into the vagina, giving rise to almost constant dribbling of urine. Gradually grew weaker. No recurrence of hemorrhage.
15	Miss M. L.	38	Skin and Cancer.	1. Carcinoma uteri. 2. Carcinoma.	Aug. 3, 1909.	Irremovable cancer of uterus.	Internal Iliacs.	1. Lessened. 2. Lessened. 3. Lessened. 4. Controlled. 5. Apparently checked. 6. Greatly improved.	Died, Oct. 23, 1910.	Severe pain and almost continuous hemorrhage were the prominent symptoms in this case. The pain was so much relieved that it could be kept under control by small doses of opiates. There was no return of the free hemorrhage. Metastases occurred in the abdomen, becoming palpable in August, 1910, and later obstructing the bowels. The improvement was striking for a year.

16	Mrs. P. S.	48	Skin and Cancer.	1. Carcinoma uteri. 2. Carcinoma.	Aug. 5, 1909.	Irremovable and extensive involvement of uterus and contiguous structures.	Internal Iliacs. Ovarians.	Negative.	Died, Aug. 9, 1909.	No difficulty was experienced at operation, and patient was returned to ward apparently in good condition. Death occurred suddenly four days later, presumably from cerebral embolism. Clinical symptoms did not indicate peritonitis
17	Miss F. F.	49	Skin and Cancer.	1. Carcinoma of pelvic organs. 2. Carcinoma.	Nov. 8, 1909.	Extensive and irremovable cancer of pelvic organs.	Internal Iliacs. Ovarians. Sacra Media.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Completely controlled until one month before death. 5. Doubtful. 6. Improved.	Died, July 11, 1910.	Patient was up and about until four weeks before she died. On June 11, 1910, there was considerable hemorrhage. Hemorrhage from this time until death.
18	Mrs. E. C.	43	Skin and Cancer.	1. Carcinoma uteri. 2. Carcinoma.	Feb. 14, 1910.	Uterus hard and firmly fixed; cervix seat of ulcerated, cauliflower-like growth; cystocele; rectocele. Cancer irremovable. Salpingo-Oophorectomy, both sides.	Internal Iliacs. Ovarians. Sacra Media.	1. Somewhat lessened. 2. Somewhat lessened. 3. Somewhat lessened. 4. Completely controlled. 5. No effect. 6. Improved.	Sent to City Hospital, March 10, 1910; died May 15, 1910.	This was not a suitable case for any operative procedure, but the severe hemorrhages and the fear of her death from hemorrhage, on the part of the patient and family, led to the ligation operation as the last hope of relief. An impending vesico-vaginal fistula developed, and the disease progressed to a fatal issue.
19	Mrs. A. L.	23	Skin and Cancer.	1. Carcinoma of pelvic organs. 2. Carcinoma.	Mar. 12, 1910.	Entire posterior wall of uterus, posterior surface of broad ligaments, down to cul-de-sac of Douglas, involved in carcinomatous process. Small intestine adherent to uterus. Several inches of intestine peeled away down to mucosa. Cancer irremovable.	Internal Iliacs. Ovarians. Sacra Media.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Completely controlled. 5. Apparently checked. 6. Improved.	Discharged, Apr. 2, 1910. Living, March 12, 1911.	Repeated severe hemorrhages had greatly weakened patient. After operation she gained flesh and strength, and was able to do light housework. She was present at the clinic, April 20, 1910. Is still living; up and around (March 12, 1911).

No.	Name.	Age.	Hospital or Private.	Diagnosis: 1. Clinical. 2. Microscopic.	Date of Operation.	Condition Found Upon Laparotomy. Palliative measures other than arterial ligation with lymphatic block.	Arteries Ligated.	Effect Upon: 1. Pain. 2. Fetor. 3. Discharge. 4. Hemorrhage. (When Present.) 5. Extension. 6. General Condition.	Results.	Remarks.
20	Miss E. N. A.	66	Skin and Cancer.	1. Malignant adenoma of vagina and uterus; epithelioma of vulva. 2. Verified microscopically.	Mar. 14, 1910.	Malignant adenoma of cervix and fundus uteri; uterine fibroids. Panhysterectomy, with removal of pelvic glands down to broad ligament. At a subsequent operation perineum and left half of vagina, up to ischio-rectal fossa, removed.	Internal Iliacs. Ovarians. Sacra Media.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Completely controlled. 5. Apparently checked. 6. Improved.	Living, March 6, 1911.	When abdomen was opened it was thought impossible to do more than ligate. After ligation, however, it was found possible to proceed as indicated. Hemorrhages had been very severe, the patient was greatly reduced in strength, and was considered by the family physician to be inoperable.
21	Mrs. S. C.	47	Skin and Cancer.	1. Carcinoma uteri. 2. Carcinoma.	Mar. 14, 1910.	Irremovable cancer of uterus; cervix ulcerated and bleeding freely. Double Oophorectomy.	Internal Iliacs. Ovarians. Sacra Media.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Completely controlled. 5. Apparently checked. 6. Improved.	Living, Feb. 24, 1911.	Hemorrhage, which had been severe, and which had reduced patient's strength, was checked. She gained in strength and weight after operation; was present at clinic, April 20, 1910, and has lived in comparative comfort for nearly a year.
22	Mrs. M. J.	42	Skin and Cancer.	1. Carcinoma uteri. 2. Carcinoma.	Apr. 18, 1910.	Irremovable cancer of uterus, extending deep into broad ligaments, involving bladder and right ureter, also rectum. Sigmoid flexure twisted on itself—almost complete volvulus; loop of sigmoid adherent to rectum; bowel almost completely obstructed. Adhesions broken up, bowel liberated, ventro-suspension performed.	Internal Iliacs. Ovarians. Sacra Media.	Negative.	Died, Apr. 22, 1911.	Patient was rendered more comfortable by relieving obstruction of bowel, but her condition was so poor that she survived operation only four days.

23	Mrs. E. P.	43	Skin and Cancer.	1. Carcinoma of pelvic organs. 2. Carcinoma.	May 2, 1910.	Uterus, broad ligaments, and base of bladder involved. Volvulus of small intestine, and kink in sigmoid, causing obstruction of bowel at two points; a loop of small intestine, which was twisted, was adherent for several inches deep in pelvis; liberated with difficulty.	Internal Iliacs. Ovarians. Sacra Media.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Completely controlled. 5. Doubtful. 6. Improved.	Discharged, May 24, 1910. Has never reported for further treatment. Lost sight of.	Hemorrhage had been very severe. This case illustrates the relief which may be given by correction of conditions other than cancer.
24	Mrs. L. K.	44	Skin and Cancer.	1. Carcinoma of pelvic organs. 2. Carcinoma.	May 9, 1910.	Irremovable cancer of uterus and contiguous structures. Sigmoid adherent to uterus. Intestine twisted in beginning volvulus. The bifurcation of the common iliac diseased. Sigmoid liberated; intestine straightened.	Internal Iliacs. Common Iliac, left side. Sacra Media.	1. Mitigated. 2. Lessened. 3. Lessened. 4. None present. 5. Doubtful. 6. Improved.	Discharged, June 27, 1910. Lost sight of.	The diseased condition of the left common iliac at the bifurcation made it fairly certain that rupture would have occurred in a short time. Ligation of the common iliac just above the bifurcation obviated this, and gave rise to no unfavorable symptoms.
25	Mrs. G. H.	34	Private.	1. Carcinoma of uterus. 2. Carcinoma.	Nov. 19, 1910.	Carcinoma of uterus; extension to other pelvic organs. Panhysterectomy (Wertheim).	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Died, Nov. 2, 1911.	General condition improved for months.
26	Mrs. C. S	56	Private.	1. Carcinoma of uterus. 2. Carcinoma.	Nov. 26, 1910.	Extensive cancer of uterus. Enlargement of pelvic glands. Chronic appendicitis. Panhysterectomy (Wertheim); appendectomy.	Internal Iliacs. Ovarians. Sacra Media.	1. Entirely relieved. 2. Checked entirely. 3. Checked entirely. 4. Controlled. 5. Apparently cured. 6. Markedly improved.	Discharged, Dec. 26, 1910. Living, July 1, 1913.	Complete abatement of symptoms. Has gained 20 pounds in weight. Perfectly well at present time.

ARTERIAL LIGATION FOR IRREMOVABLE CANCER OF PELVIC ORGANS, WITH LYMPHATIC BLOCK.—*Continued.*

No.	Name.	Age.	Hospital or Private.	Diagnosis: 1. Clinical. 2. Microscopic.	Date of Operation.	Condition Found Upon Laparotomy. Palliative measures other than arterial ligation with lymphatic block.	Arteries Ligated.	Effect Upon: 1. Pain. 2. Fetor. 3. Discharge. 4. Hemorrhage. (When Present.) 5. Extension. 6. General Condition.	Results.	Remarks.
27	Miss I. R.	54	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Dec. 7, 1910.	Seemingly too advanced for the Wertheim operation. Pelvic glands involved. Coincidental cancer of left breast, with enlarged glands in axilla. After ligation and lymphatic block, panhysterectomy (Wertheim).	Internal Iliacs. Ovarians. Uterines.	1. Entirely relieved. 2. Entirely checked. 3. Entirely checked. 4. Completely controlled. 5. Apparently cured. 6. Markedly improved.	Discharged, Jan. 21, 1911. Living, July 1, 1913.	Amputation of breast and removal of axillary glands three weeks after ligation operation. All symptoms abated. Well after two years and a half.
28	Mrs. G. D.	63	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Dec. 10, 1910.	Carcinoma of uterus. Sigmoid adherent to broad ligament. After ligation and lymphatic block it was possible to perform the Wertheim operation.	Internal Iliacs. Ovarians.	1. Negative. 2. Negative. 3. Negative. 4. Negative except venous oozing. 5. Negative. 6. Negative.	Died, Dec. 12, 1910.	Died of pneumonia and nephritis. Cause of death entirely independent of cancer. Condition of abdomen perfectly satisfactory.
29	Mrs. B. I.	32	Skin and Cancer.	1. Carcinoma of pelvic viscera (recurrent). 2. Carcinoma.	Jan. 16, 1911.	Very advanced recurrent carcinoma of pelvic viscera; contraction, causing obstruction of both ureters. By stripping up the ureters beginning hydronephrosis was relieved. Panhysterectomy (Wertheim) previously performed.	Internal Iliacs.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Doubtful. 6. Improved.	Discharged, Feb. 1, 1911. Moved away, not heard from since.	Discharged in very much better condition than when admitted to hospital. Diseased parts very much contracted. Pain in back, over kidneys, entirely relieved.

30	Mrs. A. K.	68	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Jan. 21, 1911.	Carcinoma of cervix and body of uterus. Panhysterectomy (Wertheim).	Internal Iliacs. Ovarians.	1. Negative. 2. Lessened. 3. Lessened. 4. Controlled. 5. Negative. 6. Negative.	Died, Jan. 30, 1911.	Considerable shock; died of nephritis and endocarditis. Surgical condition entirely satisfactory.
31	Mrs. A. L.	47	Skin and Cancer.	1. Carcinoma of uterus, ovaries, tubes. 2. Carcinoma.	Mar. 27, 1911.	Carcinoma of uterus irremovable. Both ovaries badly cystic.	Internal Iliacs. Ovarians. Sacra Media.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved until few weeks before death.	Died, Nov. 5, 1911.	Considerable hemorrhage before operation; none after operation. Lived seven months and nine days in comparative comfort.
32	Mrs. A. R.	35	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	April 3, 1911.	Cancer of uterus. Cervix and walls of vagina involved.	Internal Iliacs. Ovarians.	1. Lessened. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Discharged, April 27, 1911. Living, May 15, 1912. Lost sight of.	Marked improvement in all symptoms. Living in comparative comfort, when last seen, one year after operation.
33	Mrs. M. F.	45	Skin and Cancer.	1. Carcinoma of uterus and ovaries. 2. Carcinoma.	Apr. 24, 1911.	Extensive carcinoma of pelvic organs with hyperplasia of glands. Both ovaries the seat of non-cancerous inflammation evidently causing great deal of pain.	Internal Iliacs. Ovarians.	1. Lessened. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Died, Sept. 25, 1911.	Patient was rendered more comfortable after operation, particularly with regard to pain.
34	Mrs. A. F.	61	Skin and Cancer.	1. Carcinoma of pelvic viscera, with extension to abdominal viscera. 2. Carcinoma.	Feb. 8, 1912.	Extensive involvement of pelvic organs. Irremovable.	Internal Iliacs. Ovarians.	1. Negative. 2. Lessened. 3. Lessened. 4. Controlled. 5. Negative. 6. Negative.	Died, Feb. 11, 1912.	Died of pneumonia. Too advanced for operation, but patient begged that operation be done, as nothing else gave her relief.
35	Mrs. L. F.	54	Skin and Cancer.	1. Carcinoma of uterus, ovaries tubes and broad ligaments. 2. Carcinoma.	Feb. 15, 1912.	Irremovable cancer of uterus; large ulcerating mass in pelvis.	Internal Iliacs. Ovarians.	1. Controlled. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Died, Jan. 25, 1913.	Patient lived about a year after operation. Died not knowing she had cancer.
36	Mrs. J. P.	54	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Apr. 1, 1912.	Irremovable carcinoma of uterus and contiguous structures. Bladder and rectum involved.	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Died, May 24, 1912.	Considerable bladder pain, with almost continuous hemorrhage. Operation imperative on account of hemorrhage.

ARTERIAL LIGATION FOR IRREMOVABLE CANCER OF PELVIC ORGANS, WITH LYMPHATIC BLOCK.—*Continued.*

No	Name.	Age.	Hospital or Private.	Diagnosis: 1. Clinical. 2. Microscopic.	Date of Operation.	Condition Found Upon Laparotomy. Palliative measures other than arterial ligation with lymphatic block.	Arteries Ligated.	Effect Upon: 1. Pain. 2. Fetor. 3. Discharge. 4. Hemorrhage. (When Present.) 5. Extension. 6. General Condition.	Results.	Remarks.
37	Mrs. T. K.	44	Skin and Cancer.	1. Carcinoma of pelvic viscera. 2. Carcinoma.	Apr. 15, 1912.	Extensive involvement of pelvic viscera. Carcinoma right groin. Ovaries and appendix badly diseased (non-cancerous). Ovaries and appendix removed.	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Died, latter part of May, 1913.	Lived in fair condition. Able to be up and about for more than a year.
38	Mrs. B. P.	50	Skin and Cancer.	1. Carcinoma of uterus, cervix, broad ligaments and intestine. 2. Carcinoma.	May 3, 1912.	A large carcinomatous mass involving uterus, cervix, broad ligaments and intestine. Irremovable.	Internal Iliacs. Ovarians.	1. Lessened. 2. Lessened. 3. Lessened. 4. None present. 5. Negative. 6. Negative.	Died, May 13, 1912.	Died of pneumonia and nephritis.
39	Mrs. R. G.	51	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	June 25, 1912.	Irremovable carcinoma of uterus. Both ovaries involved in adhesions of inflammatory character.	Internal Iliacs. Ovarians.	1. Relieved. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Discharged, July 18, 1912. Living, July 1, 1913.	Living one year after operation. Able, July 1, 1913, to do light housework.
40	Mrs. H. S.	41	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	June 30, 1912.	Extensive involvement of uterus and contiguous structures. Irremovable. Left ovary badly diseased; non-cancerous adhesions.	Internal Iliacs. Ovarians.	1. Entirely relieved. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Discharged, July 9, 1912. Living, Jan. 1, 1913. Lost sight of.	Discharged in good condition. Living six months after operation, feeling very well. So far as patient knows is free from cancer.
41	Mrs. A. McC.	35	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Nov. 14, 1912.	Extension of carcinoma to broad ligaments. Pelvic glands greatly enlarged. Ovaries and tubes badly diseased (non-cancerous).	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. No change.	Died, Feb. 23, 1913.	Confirmed morphine habit before admission. Few weeks before death became insane and was removed to Bellevue Hospital.

42	Mrs. J. B.	38	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Nov. 18, 1912.	Irremovable carcinoma of uterus. Marked obstruction of ascending colon. Obstructions corrected.	Internal Iliacs. Ovarians.	1. Entirely relieved. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Discharged, Dec. 16, 1912. Living, July 1, 1913.	Patient better in every way. Hemorrhage ceased. At present doing light housework.
43	Mrs. D. C.	45	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Nov. 25, 1912.	Advanced cancer of uterus. Metastasis in bladder, broad ligaments, and pelvic lymphatic nodes. Vesico-vaginal fistula. Ovaries diseased.	Internal Iliacs. Ovarians. Sacra Media.	1. Entirely relieved. 2. Practically controlled. 3. Practically controlled. 4. Controlled. 5. Checked. 6. Improved.	Discharged, Dec. 25, 1912. Living, July 1, 1913.	General condition excellent; has gained in weight, able to go to work, wearing a support, since leaving hospital. Comfortable, excepting for leakage from bladder. Persistent in desire to have urine controlled. Marked cachexia entirely gone.
44	Mrs. S. M.	52	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Dec. 30, 1912.	Irremovable carcinoma of uterus. Adhesions between uterus and sigmoid corrected.	Internal Iliacs. Ovarians.	1. Mitigated. 2. None present. 3. Lessened. 4. None present. 5. Checked. 6. Improved.	Discharged, Jan. 25, 1913. Living, July 1, 1913.	General condition very much improved after operation.
45	Mrs. C. D.	36	Skin and Cancer.	1. Pronouncedly malignant tumor (carcinoma?) in cul-de-sac of Douglas, involving uterus and rectum. 2. Studied by several pathologists; classification to be determined; several tentative opinions.	Jan. 9, 1913.	Tumor filled cul-de-sac of Douglas, involving rectum and cervix. Small intestine adherent to uterus. Intestine freed and raw surfaces turned in. Panhysterectomy, removing an inch and a half of vagina and a small portion of anterior wall of rectum, size of silver dollar. Enlarged glands in pelvis removed.	Internal Iliacs. Ovarians.	1. Entirely relieved. 2. Entirely relieved. 3. Entirely relieved. 4. None present. 5. Checked, apparently. 6. Greatly improved.	Discharged, Feb. 13, 1913. Living, July 1, 1913.	Patient feels "perfectly well," has gained in weight; all symptoms have disappeared, and there are no signs of recurrence.
46	Mrs. A. F.	40	Private.	1. Carcinoma of rectum. 2. Character not determined; studied by several pathologists; several tentative opinions given. Malignant adenoma?	Jan. 21, 1913.	Mass size of hen's egg in cul-de-sac of Douglas, involving cervix in front and rectal wall behind. Piece of anterior wall of rectum about two inches square removed. Wertheim operation.	Internal Iliacs. Ovarians.	1. Entirely relieved. 2. None present. 3. Checked. 4. Controlled. 5. Checked. 6. Markedly improved.	Living, July 1, 1913.	Perfectly well at the present time.

ARTERIAL LIGATION FOR IRREMOVABLE CANCER OF PELVIC ORGANS, WITH LYMPHATIC BLOCK.—*Continued.*

No.	Name.	Age.	Hospital or Private.	Diagnosis: 1. Clinical. 2. Microscopic.	Date of Operation.	Condition Found Upon Laparotomy. Palliative measures other than arterial ligation with lymphatic block.	Arteries Ligated.	Effect Upon: 1. Pain. 2. Fetor. 3. Discharge. 4. Hemorrhage. (When Present.) 5. Extension. 6. General Condition.	Results.	Remarks.
47	Mrs. F. C.	62	Skin and Cancer.	1. Carcinoma of pelvic viscera. 2. Carcinoma.	Jan. 23, 1913.	Carcinoma of pelvic contents. Uterus irremovable. Ovaries and tubes previously removed.	Internal Iliacs.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Unchanged.	Discharged, March 22, 1913. Living, July 1, 1913.	Some abatement of symptoms, but general condition about the same.
48	Mrs. G. M. W.	55	Skin and Cancer.	1. Carcinoma of uterus and bladder. 2. Carcinoma.	Feb. 3, 1913.	Carcinoma of uterus, base of bladder. Sigmoid, which was attached to cancerous mass below, dissected away, and a piece about $1\frac{1}{2}$ inches in diameter removed.	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Doubtful. 6. Unchanged.	Discharged, March 16, 1913. Living, July 1, 1913.	Some abatement of symptoms, but general condition about the same.
49	Mrs. M. D.	52	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Feb. 6, 1913.	Uterus hard and firmly fixed; irremovable.	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Discharged, March 20, 1913. Living, July 1, 1913.	Able to be up and to do light housework.
50	Miss I. S.	52	Skin and Cancer.	1. Carcinoma of rectum; fibroid of uterus. 2. Carcinoma of rectum; fibroid of uterus.	Feb. 17, 1913.	Extensive carcinoma of rectum; fibroid of uterus. Panhysterectomy. Resection of rectum and sigmoid.	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened 4. Controlled. 5. Checked. 6. Improved.	Living, July 1, 1913.	In hospital at present time, July 1, 1913. Up and about; gaining slowly. Some incontinence of feces, but no fetor or discharge due to cancer.
51	Mrs. E. McL.	47	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Feb. 20, 1913.	Carcinomatous mass involving vagina, base of bladder and pelvic viscera.	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Discharged, May 10, 1913. Living, July 1, 1913.	Bedridden before operation; now able to be up and to do light house work.

52	Mrs. E. M.	45	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Feb. 24, 1913.	Irremovable cancer of uterus, adherent to bladder and rectum. Tubes, ovaries and appendix badly diseased, but not with cancer. Removed.	Internal Iliacs. Ovarians.	1. Entirely removed. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Discharged, March 29, 1913. Living, July 1, 1913.	"Well" at the present time. Does not know she has cancer.
53	Mrs. V. B.	45	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Mar. 27, 1913.	Irremovable carcinoma involving vagina, rectum and broad ligaments. Many abdominal adhesions. Almost complete intestinal obstruction.	Internal Iliacs. Ovarians.	Negative.	Died, March 30, 1913.	Died of nephritis, uremia, and endocarditis.
54	Mrs. G. S.	55	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Apr. 21, 1913.	Advanced carcinoma of uterus, base of bladder and broad ligaments. Irremovable.	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. Controlled. 5. Checked. 6. Improved.	Discharged, May 22, 1913. Living, July 1, 1913.	Perfectly "well" at present time, so far as patient knows.
55	Mrs. I. C.	56	Skin and Cancer.	1. Carcinoma of uterus. 2. Carcinoma.	Apr. 28, 1913.	Advanced carcinoma of uterus and pelvic glands; cystic ovary; intestinal adhesions; involvement of base of bladder and walls of vagina.	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. None present. 5. Checked. 6. Improved.	Discharged, May 15, 1913. Living, July 1, 1913.	Patient has returned to work, in very much better condition than before operation.
56	Mrs. M. W.	68	Private.	1. Carcinoma of uterus. 2. Carcinoma.	May 10, 1913.	Inoperable cancer of uterus; various adhesions ligated and divided. Appendectomy.	Internal Iliacs. Ovarians.	1. Mitigated. 2. Lessened. 3. Lessened. 4. None present. 5. Checked. 6. Improved.	Living, July 1, 1913.	Elevation of temperature before operation due to septic absorption. Now very much better.

SUMMARY OF RESULTS.

Case Number.	I. Length of Life After Operation.	II. Effect Upon Symptoms.	III. Apparent Effect Upon Growth.	IV. Effect Upon Hemorrhage.	Remarks.
1	Four years, four months.	Improved.	Retarded.	None present.	
2	Seven weeks.	Improved.	Doubtful.	None present.	
3	Six months.	Improved.	Retarded.	None present	
4	Three days.	Negative.	Negative.	Controlled.	
5	Seven months.	Improved.	Retarded.	None present.	I. Barring eight patients who died within from two to ten days after the operation, and four who were not seen after discharge from hospital, the length of life varied from seven weeks to four years and four months. Two lived two years and six months; four lived one year and more.
6	Five months.	Improved.	Doubtful.	None present.	
7	Six months.	Improved.	Retarded.	None present.	
8	Six months.	Improved.	Retarded.	Controlled.	
9	Ten months.	Improved.	Doubtful.	Controlled (after second operation).	
10	Ten months.	Improved.	Retarded.	Controlled.	
11	Five months.	Improved.	Retarded.	Controlled.	
12	Unknown.	Improved.	Doubtful.	None present.	
13	Two months.	Improved.	Doubtful.	Controlled.	
14	Ten months.	Improved.	Doubtful.	Controlled.	
15	Fifteen months.	Improved.	Retarded.	Controlled (slight hemorrhage toward last).	II. The effect upon the symptoms was negative in five cases; improved in forty-four; doubtful in two; entirely relieved in four.
16	Four days.	Negative.	Negative.	None present.	
17	Eight months.	Improved.	Doubtful.	Controlled (considerable hemorrhage one month before death).	III. The growth was apparently retarded in thirty-five cases; doubtful in eleven; negative in nine.
18	Three months.	Improved.	Negative.	Controlled.	
19	Eleven months.	Improved.	Retarded.	Controlled.	
20	Eleven months.	Improved.	Retarded.	Controlled.	
21	Five months.	Improved.	Retarded.	Controlled.	
22	Four days.	Negative.	Negative.	None present.	
23	Unknown.	Improved.	Doubtful.	Controlled.	
24	Unknown.	Improved.	Doubtful.	None present.	
25	One year.	Improved.	Retarded.	Controlled.	IV. Hemorrhage was controlled in thirty-nine cases; negative in two; none present in fifteen. In the cases in which the result was negative there was slight venous oozing, but no real hemorrhage.
26	Two years, six months.	Entirely relieved.	Retarded.	Controlled.	
27	Two years, six months.	Entirely relieved.	Retarded.	Controlled.	
28	Two days.	Negative.	Negative.	Negative.	
29	Sixteen days.	Improved.	Doubtful.	Controlled.	
30	Nine days.	Doubtful.	Negative.	Controlled.	
31	Seven months.	Improved.	Retarded.	Controlled.	
32	One year.	Improved.	Retarded.	Controlled.	

33	Five months.	Improved.	Retarded.	Controlled.
34	Three days.	Doubtful.	Negative.	Controlled.
35	Eleven months.	Improved.	Retarded.	Controlled.
36	Two months.	Improved.	Retarded.	Controlled.
37	Thirteen months.	Improved.	Retarded.	Controlled.
38	Ten days.	Improved.	Negative.	None present.
39	One year.	Improved.	Retarded.	Controlled.
40	Six months.	Improved.	Retarded.	Controlled.
41	Three months.	Improved.	Retarded.	Controlled.
42	Seven months.	Improved.	Retarded.	Controlled.
43	Seven months.	Entirely relieved.	Retarded.	Controlled.
44	Six months.	Improved.	Retarded.	None present.
45	Six months.	Improved.	Retarded.	None present.
46	Five months.	Entirely relieved.	Retarded.	Controlled.
47	Five months.	Improved.	Retarded.	Controlled.
48	Five months.	Improved.	Doubtful.	Controlled.
49	Five months.	Improved.	Retarded.	Controlled.
50	Four months.	Improved.	Retarded.	Controlled.
51	Four months.	Improved.	Retarded.	Controlled.
52	Four months.	Improved.	Retarded.	Controlled.
53	Three days.	Negative.	Negative.	Negative.
54	Two months.	Improved.	Retarded.	Controlled.
55	Two months.	Improved.	Retarded.	None present.
56	Seven weeks.	Improved.	Retarded.	None present.

NOTE.—Of the first series of twenty-four cases four patients were traced up to 1911. Of these, No. 1, operated Sept. 26, 1906, was alive and well* March 12, 1911; No. 19, operated March 12, 1910, was alive and well March 12, 1911; No. 20, operated upon March 14, 1910, was alive March 6, 1911, but has died since; No. 21, operated March 14, 1910, was alive and well Feb. 24, 1911. Attempts made in December, 1912, to trace these patients proved futile except in No. 20.

Of the thirty-two cases comprising the second series twelve died, three were lost sight of, and seventeen were living July 1, 1913.

* Unless otherwise indicated, "well" refers to the condition as reported by the patients. They are kept as nearly as possible ignorant of the real condition, and in many cases so far as they know are "well."

RESPIRATORY SYSTEM

Tracheostomy is employed for the relief of obstruction in cases of irremovable cancer of the larynx or other structures high up in the neck. The artificial opening must be below the disease.

ALIMENTARY SYSTEM

Palliative procedures, directed chiefly toward the relief of obstruction caused by irremovable cancer, are applicable to various portions of the alimentary tract.

Esophagostomy is resorted to in advanced cancer of the mouth, tongue, or pharynx, particularly if the disease is sufficiently extensive to cause obstruction. The artificial opening should be made as low down as possible, with the hope of escaping extension.

Gastrostomy is advocated by some surgeons, and deprecated by others, for the relief of obstruction in cancer of the pharynx, esophagus, and cardiac end of the stomach. It is held by some that the relief is not sufficient to warrant the operation. Others call attention to the possibility of an error in diagnosis, by which a patient is unnecessarily condemned to this mode of taking nourishment. Excluding mistakes in diagnosis, it cannot be gainsaid that a patient should not be allowed to die of starvation when there is a possibility of relief by gastrostomy.

Gastro-enterostomy, or anastomosis between the stomach and some portion of the small intestine, is advocated when cancer of the stomach causes obstruction at the pyloric outlet.

The terms "anterior" and "posterior" are employed when the union is made to the anterior or posterior wall of the stomach.

The operation is more specifically designated "gastro-duodenostomy," or "gastro-jejunostomy," when the union is made between the stomach and the duodenum or the jejunum, respectively.

Colostomy, or the making of an artificial anus, is employed by some surgeons for the relief of obstruction in cancer of the colon. The opening may be placed in the lumbar region (lumbar colostomy), or in the right or left groin (right inguinal colostomy, left inguinal colostomy, or sigmoidostomy, respectively).

When the operation is carefully performed and a properly constructed pad is employed, the colostomy opening may prove very satisfactory. In many instances, however, the artificial anus does not work well, the support is not properly adjusted, and leakage is the inevitable result.

"Short-circuit."—In many cases in which colostomy is advocated by some surgeons, a short-circuiting operation would answer the purpose more satisfactorily. By this means the affected portion of the gut is thrown out of use by uniting the intestine above and that below the disease. The point of union should be at as great a distance as feasible from the growth, in order to allow the patient a considerable length of life before the disease again encroaches upon the caliber of the intestine.

Colectomy, or the removal of a portion of the colon, may be done even in the presence of apparent metastatic disease in glands which are high up, perhaps under the liver. The involvement of the glands, however, may be inflammatory, and removal of the colon, with end-to-end anastomosis, or with closure of both ends and anastomosis between the ascending and the descending colon, may effect a cure of the malignant disease in the gut. In one case in which I performed this operation six years ago there was apparent extension of the cancer into the glands back of the liver. These were distinctly enlarged, but could not be removed. The fact that the patient is well after six years leads to the conclusion that the glands were not the seat of malignant, but of inflammatory, involvement.

URINARY SYSTEM

Cystostomy, or artificial opening in the bladder, is indicated when a malignant neoplasm of the bladder, urethra, or prostate, causes obstruction to the passage of urine from the bladder. The situation of the growth determines whether the opening should be suprapubic or perineal.

Nephrotomy, or drainage of the kidney through an opening in the loin, is employed when both ureters have become closed by the encroaching malignant growth. The right kidney, which, as a rule, is the last affected, should be drained first. The left kidney, which is generally more extensively involved by the time anuria results, need not be opened so long as the other functionates, one active kidney being sufficient for the maintenance of life during the remaining short span.

Ureteral transplantation may be resorted to when malignant disease in the vicinity tends to block off the drainage of urine from either kidney. The ureter of the affected side may be transplanted into the intestine, or into the loin. The latter procedure is preferred by many surgeons, because of the ever present danger, in the former case, of infection of the kidney and death from pyelo-nephritis.

BILIARY SYSTEM

Cholecystostomy—the creation of a permanent opening into the gall-bladder through the abdomen—or *Cholecyst-enterostomy*—the making of an artificial opening from the gall-bladder to the intestine—may greatly relieve the extreme jaundice which results when the passage of bile is interfered with by cancer of the head of the pancreas, the bile papillæ and biliary ducts, or the glands in the portal fissure.

I had a case two years ago in which there was cancer at the head of the pancreas, with damming back of the bile in the gall-bladder. The jaundice was extreme, and the suffering of the patient from the intense and persistent itching of the skin, which could not be relieved, was almost intolerable. Cholecyst-enterostomy gave great relief, and the patient lived, in a fair degree of comfort, for two years.

SUMMARY

From a study of the foregoing special methods it is evident that by various modifications of technic, and by plastic and palliative measures, the chances of the cancer patient to-day for permanent cure, for operation with a minimum of deformity, and for increased comfort when cure is no longer to be expected, are far greater than they were a few years ago. The surgery of the future will doubtless warrant, in still greater measure, the hope that "springs eternal."

SECTION XII

IRREMOVABLE CANCER

INTRODUCTORY REMARKS

In other sections we have dealt with the earlier and more hopeful stages of cancer. We come now to a general consideration of the more advanced and less hopeful stages, to which the term "inoperable" is so commonly and sometimes so carelessly applied. (Special methods which may be employed in the surgical treatment of advanced cancer of certain regions are discussed in Section XI, Chapter 2.)

For purposes of clarity, particularly with reference to treatment, it has been my custom [1] to classify advanced cancer under the following heads: (1) *Seemingly* irremovable; (2) operable, but irremovable, yet curable; (3) operable, but irremovable and incurable; (4) inoperable, irremovable, and incurable.

A casual consideration of this classification suggests that the word "inoperable" in reality applies, in the majority of instances, only to the very last stage of the disease, and to a minority, perhaps, of advanced cases. There never is a time, in the course of the disease, when it would be permissible, from either a surgical or a humanitarian point of view, to add in any degree to the already overwhelming burden of mental and physical suffering which usually accompanies advanced cancer, without a distinct hope of compensatory good. The diagnostic skill of the surgeon is oftentimes taxed in the attempt to decide whether the patient shall be consigned to the category of the inoperable, or whether further surgical measures are justified.

When, therefore, the surgeon is called upon to treat a patient who, for any reason, is unmistakably the victim of inoperable cancer, the question may justly be asked, "What more can surgery do?" So far as the cancer itself is concerned the answer must undoubtedly be, "Nothing." But what about the

[1] Bainbridge, W. S.—"Irremovable Cancer," *N. Y. Med. Jour.*, October 3, 1908.

patient? Shall we fold our hands and say, "All has been done that can be done by surgical means; opiates and other palliative measures are all that may be employed; death only can bring relief?" Emphatically, No! Surgery may still have a purpose to fulfil.

Cancer, in the majority of cases, is not an acute disease, but one which kills by slow and often painful processes. In the class of cases now under discussion, relief from pain may be given by surgical methods. This may be done through the treatment of indirect conditions caused by the cancer.

The various surgical procedures which aim solely at the prolongation of life and the amelioration of pain and other symptoms have been called "emotional surgery," and those who advocate the methods have been pronounced "emotional surgeons." Perhaps the allegation is correct; but I feel sure that only those who are afraid of increasing the number of death certificates, or those who are callous to human suffering, will refuse to accord to these unfortunate patients whatever modicum of relief surgery can afford.

Year by year more is being accomplished, by both surgical and non-surgical means, for the victims of irremovable cancer. In addition to various special surgical methods (see Section XI, Chapter 2, X-rays, fulguration, thermopenetration, thermoradiotherapy (see Section X, Chapter 2), and numerous other kinds of treatment are now being employed for the relief of patients who have formerly been consigned to the fate of "the usual palliative measures"—cleansing applications, dressings, opiates, etc.

Among many, however, there is still a tendency to move in the line of least resistance, and to resort to this palliative treatment where more radical and effective measures should be employed. The physician, and those who compose the most immediate world of the victim of advanced cancer, are prone to consider the case incurable. Looking upon such an individual as a "cancer case," for whom little, if anything, can be done, they often fail to realize that the patient, while suffering from cancer, may at the same time be the subject of any one, or a combination, of other ills.

In consequence of this attitude, when anything at all is done, the *cancer,* rather than the *patient,* is treated. This mental attitude is quickly interpreted, and the gloom of the physician, attendants, and relatives is reflected upon the patient, giving thus an added hopelessness to the situation and hastening the ultimate outcome of the disease.

Let us advocate a humane and skilful effort, by all possible surgical or other means, to relieve the concomitant symptoms of the advanced stages of cancer, rather than be content with the "usual palliative measures." Conservative treatment, in the broadest acceptation of the term, is surely the adaptation of the measures employed, be they surgical, electrical, medical, or what not, to the needs of the individual. This of necessity involves, not only the treatment of the cancer itself, but the correction, when possible, of all concurrent pathological conditions which may have been caused by, or which may complicate, the malignant disease. It also necessitates careful consideration as to whether the case is operable or inoperable.

In this connection it may be interesting to note the classification of "inoperable" cancer given by Morris:[1]

"The term 'inoperable' means that the disease cannot be entirely eradicated, or permanent immunity hoped for, by a cutting operation, or by actual cautery, or any escharotic aiding the knife. It does not imply that malignant disease is of constitutional as distinct from local origin, and that as such it is ineradicable. On the contrary, I take it for granted that cancer is at first, and so far as rodent cancer is concerned, throughout a local disease. But even on this view there are four groups of inoperable cases. They are: (1) primary cancer affecting inaccessible parts and organs; (2) primary cancer which, though originating in an accessible part or organ of the body, has been allowed to extend beyond the limits within which an operation is prudent and complete removal possible; (3) certain cases of acute diffuse carcinoma and very rapidly growing or widely infiltrating new growths of exceptionally virulent character; and (4) recurrent cancer, where the disease has recurred in multiple metastatic foci or in parts beyond the limits of removal. Many of the cases included in these groups are submitted to operation for the purpose of palliating symptoms or prolonging life. Hence the term 'treatment' as applied to inoperable cancer means one of two things: (1) the employment of remedies and methods other than the knife, to cure, ameliorate, or retard the disease, as well as to prevent relapses after its removal; or (2) the employment of the knife to give relief from pain and to prolong life, to restore function, and otherwise to make the patient's condition more tolerable."

[1] Morris, Sir Henry, Bart.—"The Treatment of Inoperable Cancer," *The Lancet*, October 3, 1908.

SEEMINGLY IRREMOVABLE

The cancer *per se* may be easily amenable to operation, while, for various reasons, it may be *seemingly* irremovable. In such instances it may perhaps be only natural to place the patient in the category of the inoperable, and eventually the incurable. A careful study of the individual case often reveals the fact that it belongs to neither category, for the following reasons:

(1) The patient's condition in other respects may render the cancer seemingly irremovable. If the contraindicative condition is temporary, as in the case of concurrent acute affections, proper measures for correction should be instituted. A cancer which is seemingly inoperable and irremovable may be rendered both operable and removable by proper care of the patient.

If the general condition of the patient, from whatever cause, is such as to render precarious the administration of a general anesthetic, with the shock of a major operation; and if local anesthesia or spinal analgesia are impossible or inadvisable, time must be given to the general upbuilding of strength and bodily resistance. It is necessary in such cases to exercise judgment in the matter of how long operative procedure may be delayed without menace to the patient's life from the malignant growth. It may at times be the part of wisdom to run surgical risk in the operable stage of cancer, complicated by other conditions, rather than to delay too long and allow the patient to pass into the irremovable, even though operable, stage.

It is just here that surgeons may often err. The cancer obscures, in their eyes, all other conditions, and a patient who may be easily amenable to operative procedure after due attention to other conditions, is pronounced "incurable," "inoperable," or the cancer, "irremovable." On the other hand, the patient may be subjected to the risk of operative procedure before due attention is given to the concurrent conditions, life being thus unnecessarily endangered. The ability to carry the patient safely past the dangers of too early operation on the one hand, and the fatal error of too long-delayed surgical intervention on the other, entails a certain intuitive sense, which comes only through large personal experience in the treatment of malignant disease, and which cannot be fully explained or imparted to others.

(2) Malignant new growths are sometimes seemingly irremovable when they are superimposed upon lupus erythematosus, lupus vulgaris, or syphilis. The author has seen a

few cases of cancer of the breast, complicated by uterine fibroids causing hemorrhage, which have been pronounced irremovable, the supposition being carelessly reached that the uterine condition is cancerous and of a too advanced stage to permit of operation.

(3) Concurrent complications in the neighborhood of the cancer may lead to the simulation and diagnosis of an irremovable growth. There may be tissues in the neighborhood which are involved in inflammatory reaction; neighboring glands may be the seat of pus collections; and various other complications may for a time obscure the prognosis with reference to the cancer. Under such circumstances, because of the seeming hopelessness of the condition, both the complication and the malignant disease are neglected until the cancer in reality becomes hopeless.

(4) Septicemia or sapremia, arising from causes only indirectly associated with the cancer, or even having no relation to it, may so overwhelm the patient, because of the profound intoxication of the system, and the consequent lowering of resistance, as to lead to the belief that the cancer is irremovable. Removal of the cause and the promotion of elimination will in some cases so completely overcome the complicating condition as to render the cancer easily operable.

(5) Cases are sometimes consigned to the inoperable and irremovable class because the risk from operative procedure seems too great to be incurred. This conclusion may be based upon the extent of the involvement, or upon the patient's lowered vitality and lessened resistance. In many instances the risk undoubtedly is too great to warrant operative procedure, but the surgeon should not be too easily discouraged by either the extent of the involvement or the unfavorable condition of the patient. It is possible in many instances, by what has been called "appallingly radical surgery," to literally cheat the grave of its prey for many months and even for years.

(6) Another factor which may lead to the verdict "irremovable" is an unqualified mistake in diagnosis. An extensive gummatous involvement of the tongue, for example, has been mistaken for cancer, and, even after removal of the tongue, an unfavorable prognosis as to cure has been rendered. Such a mistake, with our present methods of diagnosis, is mentioned merely because, inexcusable as it is, it does occur. (See Section VII, Chapter III, p. 200.)

OPERABLE BUT IRREMOVABLE, YET CURABLE

Strictly speaking, cancer is "curable" only in so far as it is removable, inasmuch as we possess no known agency by which we are able definitely to cure the disease when left *in situ*. In effect, we are justified in saying we cure a cancer which is subjected to early and complete removal, as judged by a reasonable period of non-recurrence. There are other circumstances, however, under which it may be said that cancer is cured, or indefinitely held in abeyance, and to some of these attention is now directed. Spontaneous retrogression or "cure" is not under discussion here. This subject is considered elsewhere. (See Section VI, p. 172, and Section VII, Chapter 1, p. 186.)

A limited number of cases of advanced cancer have been cured, or at least held in abeyance for a number of years, by removing as much as possible of an irremovable growth and instituting other measures, by the aid of which nature seems able to cope with the malignant process, holding it in check so completely that the disease may be said to have been cured.

Such an instance is Case No. I of the series reported by Dawbarn.[1] The operation of carotid excision was performed on June 1, 1895. On going to press, March, 1903, eight years later, the patient was perfectly well, and when last heard from, in 1907, was still in perfect health. The condition for which the operation was performed was round-celled sarcoma involving the nasopharynx, filling both nares, rendering deglutition and respiration difficult, and interfering with articulation. The growth caused severe headache and dizziness. When a case of this character is reported as well twelve years after operation it is reasonable to say that a cure was effected, despite the fact that the cancer was irremovable.

Sometimes partial removal of diseased tissue results in cessation of growth and apparent cure. An illustrative case in the author's experience is that of melanotic sarcoma on the wrist of a man, with extension into the axilla and upward to the clavicle, filling Mohrenheim's space above, and completely surrounding the subclavian vein to its entrance into the chest. The tumor on the wrist was excised, and the axilla cleared out, but it was impossible to remove all the diseased tissue. The outer surface of the ribs was scraped, and the external intercostals, which were diseased, were curetted for some distance. The operation was performed in December, 1902, and in Janu-

[1] Dawbarn, Robert H. M.—"Starvation Treatment of Malignant Growths by Excision of the External Carotids," 1903, p. 9.

ary, 1914, the patient was perfectly well, with free use of his arm. No other form of treatment was employed in this case.

OPERABLE, BUT IRREMOVABLE AND INCURABLE

A large proportion of cases of advanced cancer come under this category. It may be impossible to remove all the diseased tissue, yet the case may be amenable to a variety of surgical procedures for the relief of pain and prolongation of life.

The management of these cases may be considered under the following heads: (1) treatment of indirect conditions caused by or complicating the cancer; (2) treatment of the cancer *per se;* (3) treatment of the patient.

Treatment of Conditions Caused by or Complicating the Cancer.—A malignant tumor may give rise to various conditions which call for relief by surgical interference quite apart from that which involves the cancer. It may, for example, cause obstruction of the nose, of the esophagus, of the stomach, or of any portion of the intestinal tract, necessitating, as the case may be, tracheotomy, esophagostomy, gastrostomy, enteroenterostomy, colostomy, short-circuiting, etc. In cases of obstruction of the bladder, suprapubic cystostomy or perineal drainage may be necessary. An irremovable tumor in the axilla, either a primary growth or, more frequently, a recurrence following mammary cancer, may, by pressure upon the lymph vessels, cause marked and painful swelling of the arm, the resulting condition being sometimes known as "brawny arm," or "big arm," which may be relieved by lymphangioplasty. Paracentesis of the pleura in cancer of the lung and pleura, and of the abdomen in certain cases involving the abdominal viscera, and decompression operations in cases of cerebral tumor, relieve pressure and other concomitant symptoms. The malignant growth may press upon nerves, giving rise to the most excruciating pain. When it is possible to reach and cut the nerves thus pressed upon, great relief may be obtained. Pressure symptoms may be relieved by arterial ligation with lymphatic block.

It is impracticable in this connection to call attention to all the possible complications which may be encountered in the treatment of advanced cancer. The surgeon must be able to recognize them as they arise, and to cope with them in the most advantageous manner. Above all, he should not fall into the error of neglecting remediable conditions merely because they complicate advanced cancer. The special technic of the most important palliative procedures is given in Section XI, Chapter 2.

Treatment of the Cancer Per Se.—Various methods have been employed in the attempt to arrest the growth of the cancer and to alleviate the symptoms which are the direct outcome of the disease. Many agents and methods which have been employed with the hope of effecting a cure have been found to do no more than serve as palliative measures, while many others have been used solely with the latter object in view. Certain methods are applicable only in cases of irremovable cancer of certain localities. Notable instances are lymphangioplasty in "brawny arm," arterial ligation for advanced cancer of the neck and face and of the pelvic organs, and thermoradiotherapy in cancer of various regions. Aside from such indirect measures, nothing remains to be done, so far as the cancer itself is concerned, except to keep the fungating or raw surfaces clean, to lessen fetor and discharge, and to prevent irritation.

Treatment of Patient.—In addition to the proper recognition of, and attention to, concurrent affections, acute or chronic, which may complicate malignant disease in the advanced stages, and to the requisite treatment of the cancer *per se,* it is important to treat the *patient.*

It is of the greatest moment to the mental and physical comfort of the patient that the hygienic conditions, both of the body and of the external surroundings, be the best possible. A varied dietary of wholesome and appetizing food, an abundance of fresh air and sunshine, and a sympathetic and cheerful attitude on the part of nurses and other attendants, will materially assist in the fight for life.

It is necessary to combat the evil effects of the cancerous process upon the system by the administration of tonics, digestives, and such measures as may be necessary to facilitate elimination. It is of the utmost importance that the emunctory organs be kept active. In many instances the patient is cachectic as much or more from the locking up of the secretions by physical inactivity, by insufficient or improper food, and by morphia, as by the disease itself.

INOPERABLE, IRREMOVABLE, INCURABLE

When surgical procedure offers no further hope of relief, when the various medicinal agents have failed to check the ravages of the disease, when electrotherapy, radiotherapy, serumtherapy, and the various other methods have been tried and found wanting, what then? The patient is now surely inoperable, and the cancer is irremovable and incurable? The sole aim of treatment is now the alleviation of the suffering of the patient and of the discomfort of those about the unfortunate one. It is well known that many of these sufferers live for years with what the laity call "eating cancer"; these years, or whatever length of days remains, should be made as comfortable as possible. Now, as much as ever, the *patient* should be treated.

Institutional Care.—When the patient has reached the final stage of cancer, unless he is the fortunate possessor of sufficient means to procure the equivalent of hospital service, institutional care may be necessary. It is too much to expect the average family to devote the requisite attention to such patients, but hitherto it has been impossible for the humane part of the community to provide proper care for more than a minute proportion of this most unfortunate class. By reference to the section which deals with hospitals and other institutions for the care of cancer patients (Section XIII) it will be seen how inadequate even yet is such provision throughout the civilized world.

Mental Condition.—However hopeless the physician and attendants may be regarding the outcome of a given case, the patient is often hopeful. By nurturing this spark of courage the remaining span of life may be rendered more bearable for the unfortunate victim. Even when the patient shares the general gloom, and, as is sometimes the case, begs to have the end hastened, the physician is not allowed by ethics or law to resort to euthenasia. In such cases great mental relief comes with the realization that those in attendance manifest a willingness to do everything possible for the comfort and welfare of the sufferer. In many instances, in institutions, the patient's mental condition is improved, and likewise the physical well-being, by the régime, and by the consciousness that the loved ones at home are relieved of responsibility and care.

The following cases, recently under my charge, are cited to show how the exercise of consideration in the care of patients suffering from advanced cancer may relieve suffering and apparently prolong life, and how, in some instances, when hope is ruthlessly snatched away, the end may be hastened.

Four patients, in the same ward, were suffering from advanced cancer. The first was cancer of the breast. This patient had had recourse to "faith cure," and later had been treated with X-rays. Upon admission to the hospital there was an immense ulcerating cancer below the right shoulder and back of the axilla, the fetid mass extending over the right chest. The arm was enormously swollen. No surgery, not even lymphangioplasty, had been employed. The surfaces were cleansed with yeast and later treated by thermic coagulation. After eight months the patient was much better than when the treatment was begun. The cancer was not cured, but the mixed infection was controlled. The woman was not promised a cure, but was assured that she could be helped.

In the next bed was a woman who was brought in on a stretcher, practically bleeding to death from far advanced pelvic cancer. The "starvation ligature" was employed, and in a few weeks the patient was up and about the ward. The fetid discharge was checked, the hemorrhage was controlled, and the pain was greatly mitigated. Six months after leaving the hospital she was going regularly for treatment by means of thermoradiotherapy, was living in comparative comfort, and still hopeful.

In the third bed was a woman who was suffering from advanced cancer of the ovary, involving the pelvis, irremovable, and complicated by intestinal obstruction. Laparotomy was performed and the intestinal obstruction relieved. The cancer was not cured, but the patient was discharged greatly improved, and was going regularly for thermoradiotherapy three months after the operation.

In the fourth bed was a young woman, the mother of two children, who had been brought into the hospital on a stretcher in a pitiable condition, suffering with cancer of both breasts. Examination revealed that, while the cancer of the breasts might have been operated upon, the case was complicated by an extensive cancer of the left lung. After a few treatments with thermoradiotherapy she was able to be up and about the ward, breathing much improved, pain and discharge greatly lessened. The family insisted that she should know her true condition. On Tuesday she was told the exact facts, at once lost all hope, and was buried on the following Sunday.

The above observations are not in keeping with the experience of all surgeons. Sir Alfred Pearce-Gould,[1] for example, whose experience covers thirty years on the surgical staff of the Middlesex Hospital, London, says:

"The mental quietude the patients usually exhibit is quite striking, and I believe it has important physical effects. In its absence we usually find ourselves unable to relieve these patients as we are accustomed to do. I have often heard from the sister of the ward that 'No, so-and-so has not settled down

[1] Gould, Sir Alfred Pearce-.—"The Treatment of Inoperable Cancer," *The Lancet*, January 25, 1913, p. 216.

yet,' and this is given as the explanation of physical ills. This 'settling down' is an important condition of physical well-being in these poor sufferers; it means more than getting accustomed to new and strange surroundings, to the getting over the separation from 'home'—a word that is as sacred and as full of meaning upon the lips of a poor hospital patient as from anyone. It means the absence of anxiety about husband or wife and children, the confidence that one's own wants will be met even to the end, and I have come to think that the knowledge of the incurable nature of their illness is also, as a rule, not without its helpful influence. Here, I know, I am making a statement that will not win general acceptance. I am very often requested by the friends of patients not to let them know that they are suffering from cancer, and such a request one is bound to respect. But, all the same, I must say that in my experience the knowledge of the real state of affairs has very rarely seemed to do harm, and in the late stage of the disease, when curative measures are not to be thought of, and palliation is our function, it has seemed to do great good."

In this matter, as in all others, the patient must be treated, mentally as well as physically, according to individual need. My own experience has convinced me that in a large proportion of cases of advanced cancer, particularly of the abdominal and pelvic organs, even when this is secondary to external cancer which has been removed, it is possible to conceal, in part, the real state of affairs from the patient, and thus to obviate, in a measure, the mental suffering and anxiety which would otherwise attend the last days of life.

It has been observed by physicians and nurses in charge of wards for incurable cancer that much of the mental and physical discomfort of these patients during the first few days after admission is the result of breaking them of the morphin habit. During this period of "settling down" aspirin, salol, and similar agents are most helpful. After a few days the patient gradually ceases to depend upon or to expect morphin, and the mind then becomes more at rest. The general physical improvement which so often follows the more or less complete elimination of morphin, reacts favorably upon the mental condition, this, in turn, upon the physical, and thus the patient is often enabled to live through the remaining time of life in relative peace and comfort.

Physical Condition.—As the malignant disease makes ever increasing inroads upon the vitality of its victim, there is more and more need for attention to the general physical condition. The emunctory organs must be kept active by the regulation of the diet to suit the needs of the individual, and by the administration of the necessary tonics, digestives and medication which facilitates the eliminative processes of the body. This is particularly important in patients who are markedly cachectic, and in those to whom morphin is given for the alleviation of pain. Attention has already been called to the fact that the patient is often cachectic as much or more from the locking up of the secretions by physical inactivity, by insufficient or improper food, and by the continued administration of morphin, as from the effects of the disease itself. This is particularly true in the last stages. Physical fatigue and mental unrest add to this difficulty. Constipation is especially to be noted and obviated. In uterine cancer discomfort is very greatly increased by the pressure from a lower bowel packed with fecal matter. Drastic purges should not be given, particularly in involvement of the bowel. As a rule, mild aperients and bland enemata will answer the purpose. If not, attention must be more closely directed toward the diet and general hygienic surroundings.

The general physical well-being of the victim of advanced cancer is improved by an abundance of fresh air and sunshine. How often is the poor sufferer confined in a small, dark, poorly ventilated room, where he is almost literally suffocated by the foul air which his own disease has vitiated!

Diet.—A great deal has been written with reference to the influence of diet in the production of cancer and in the stimulation of the process once it has been initiated. Too much of this or too little of that constituent, certain articles of food, overindulgence in food in general—these and many other ideas with reference to the effect of diet on cancer have been proposed as having greater or less significance. Whatever importance may be attached to diet in relation to the cause of cancer—and none has been established,—such significance cannot apply when the disease has reached the inoperable, irremovable, and incurable stage. It is to be considered now merely from the point of view of maintaining strength, of aiding elimination, and of stimulating appetite. In order to accomplish these purposes the diet should be wholesome and varied. No particular article of food or drink need necessarily be omitted, and no particular constituent of any article of food, given in moderation, may be said to be harmful. Salt, for example, has been condemned by some, notably by Beard in connection with the enzyme treatment. If, however, it were known to exert a deleterious influence upon the course of the disease in the early stages—which has not been proved,—in the advanced stages, when the appetite is none too good, the elimination of any such effect would be more than counterbalanced by the insipidity of a salt-free diet.

Many have condemned as positively harmful the use of alcoholic beverages in any stage of cancer. Gould,[1] for example, holds that alcoholic stimulants of all kinds are, as a rule, to be avoided, and that the free use of alcohol adds greatly to the activity of the disease. My own experience is that it may be taken in moderation, with the food, serving merely as an appetizer. There is almost invariably a tendency to hyperacidity in these cases, hence alkalies and alkaline waters should be given. Intestinal antiseptics and antacids are helpful. If the hyperacidity is unusually pronounced, the diet may be modified accordingly.

Pain.—Pain may be controlled to a certain extent by morphin, to be counterbalanced always by something to offset its untoward effects. If there is sweating, atropin may be given with the morphin, or, if it is to be given over long periods of time, it may be administered in the form of the United States or the British solution, with the elixir of lactopeptin. Phenacetin, 10 to 15 grains twice daily, will sometimes be sufficient to control severe pain and to make the patient fairly comfortable. Aspirin, salol, antipyrin, and acetanilid may also be used. The depressing effects of the coal tar products should be modified by stimulants.

Care of Ulcerating Surfaces and Fungating Masses.—Bearing in mind the fact that the discharges from broken-down cancer are often rendered more offensive by the action of putrefactive or pyogenic organisms, attention should be directed to keeping the surfaces clean by the use of the various antiseptic ointments and washes. Deodorizers, ozone, incense, etc., may be used in the room to render the atmosphere less disagreeable.

Fungating masses should be kept clean by frequent dressing. The galvanocautery, thermocoagulation, zinc chlorid paste, lotio pancreatis, yeast poultices, and various other local applications will help to keep the surfaces clean and to lessen fetor. Acetone, peroxid of hydrogen, permanganate of potassium, and sanitas are useful for this purpose. It must not be forgotten, however, that local applications, particularly pastes, may tend to erode blood vessels and thus give rise to severe and perhaps fatal hemorrhage. Where the cancer has eaten its way through the tissues, leaving openings, as in the pharynx or base of the mouth, the compound tincture of benzoin with nosophen or

[1] Gould, Sir Alfred Pearce.—*Loc. cit.*
See also: "The Bradshaw Lecture on Cancer," 1910, p. 53.

aristol (Bainbridge's modification of Whitehead's shellac [1]) may be used to plug the openings. This tends to hold the parts in position and makes a very good antiseptic dressing. Adrenalin chlorid is also useful for the control of hemorrhage. Terchlorid of antimony will help to check hemorrhage and to lessen fetor in uterine cancer after the vessels have been ligated and as much as possible of the diseased tissue removed.

In uterine cancer sloughing or fungating masses should be removed by means of the curet, care being taken not to injure the peritoneum, bladder, ureter, or rectum, which, in the presence of extensive involvement, may be easily penetrated. Non-irritating antiseptic douches should be employed frequently. Where there is danger of hemorrhage it is well to have the fluid hot. In cancer of the rectum it is especially important that cleanliness be maintained by the removal, by means of douches, of particles of fecal matter and discharge.

In cancer of the mouth particular attention should be given to cleanliness, not only for the purpose of rendering the patient more comfortable and of lessening fetor, but in order to prevent the swallowing, with the food or saliva, of quantities of cancerous material and the products of mixed infection. The frequent use of mild mouth washes, particularly before and after meals, the removal, by means of pledgets of cotton, of particles of food, mucus, or discharge, the extraction of loose or decayed teeth and sequestra, and the removal of sloughs, will add greatly to the patient's comfort.

SUMMARY

It is impossible here—and, indeed, it is unnecessary—to attempt an enumeration of the many attentions which it is possible, feasible, and humane, to bestow upon the victim of inoperable, irremovable, and incurable cancer. The conscientious physician and nurse will recognize and endeavor to supply the needs of each individual.

Irremovable cancer is a difficult, and many times a discouraging, condition with which to deal, and this particular field is not very alluring to the surgeon who is trying to keep down his mortality records and to swell the list of his surgical successes. But the physician or surgeon who fails to do the very utmost for such patients, or who does not refer them to those who will give them proper attention, is not true to the spirit of the Hippocratic oath.

[1] This consists of twice the strength of compound tincture of benzoin, with nosophen or aristol instead of iodoform.

SECTION XIII

INSTITUTIONS FOR THE CARE OF CANCER PATIENTS

The care of the cancer patient is a problem which should be considered apart from the investigation of the disease.

In view of the fact that perhaps the majority of the general hospitals throughout the world receive for operation only those cases of cancer ordinarily classed as "operable," we have included in this discussion only those hospitals and "homes" which care for so-called "incurable" cases. "Quack" institutions, of course, are not considered.

No attempt is made to give a complete catalogue of institutions which open their doors to the victims of incurable cancer. The purpose of this section is rather to emphasize the need of larger and better facilities than now exist for the care of this class of patients.

Peculiar needs for treatment, care, and encouragement mark the life of the incurable cancer patient. Wealth can supply these needs, but what does poverty face in this regard? What possibilities are open to the poor for the proper care of those so afflicted?

With a view to answering the above questions, the Research Department of the New York Skin and Cancer Hospital undertook a fairly comprehensive canvass of the institutions of New York City and vicinity two years ago. The results of this investigation, together with similar data concerning certain European cities, are given below.

IN EUROPE

In Europe the past half century has witnessed an enormous increase in the number of general hospitals, and in the number of beds in the older hospitals. There has been also a great increase in the number of surgical operations, many of which have been made possible by anesthetics and asepsis. This applies especially to cancer. In order to discover, and if possible to remove tumors, surgery has gradually progressed to every organ of the body, even to the brain and spinal cord. On looking back over this development of hospitals and surgery, one would expect to find a corresponding increase in the amount of special provision for cancer patients; it is astonishing, therefore, to note that this is not the case.

Great Britain.—In England two of the institutions which provide especially for cancer patients antedate the modern development of surgery, and only three have been added. No doubt this is largely due to the increased provision for the treatment of this disease in general hospitals, and in hospitals for diseases of women. Very little provision is made, however, for those actually dying of cancer. Some of the poor obtain admission to workhouse infirmaries or other poor-law institutions, and the more fortunate obtain admission to some "Hospice," "Home for the Dying," or "Home for Incurables." Notwithstanding the fatal significance of these names, the merciful provision of some care and comfort for those dying of cancer must indeed seem a blessing to those who can obtain any kind of hospital attention while awaiting the inevitable end. The majority of those who succumb to cancer, however, die outside hospitals, in their own homes, or in those of relatives.

Why is this state of affairs tolerated? The answer is that there has arisen no need for segregation, as in epidemic diseases, no evil effects having been produced upon the community by allowing cancer patients and those dying of cancer to mix freely with the rest of the population. If there are from 40,000 to 50,000 deaths from cancer in a year in the United States, then there are from 120,000 to 150,000 living who are suffering from the disease, all the year round. There is no means of estimating in this country what proportion receives hospital treatment or dies in institutions. Only for England are such figures available. In that country of 15,589 males and 20,313 females dying of cancer, 4,618, or 30 per cent. of males, and 3,971, or 20 per cent. of females, died in institutions. In London the proportions so dying are higher than in the country towns, smaller cities, and rural districts.

The institutions devoted solely to the treatment of cancer in England are only five in number, providing a total of only 200 beds, very few of these being set aside for patients remaining an unlimited time, or "until relieved by art or released by death," as in the case of special wards of the Middlesex Hospital, the pioneer institution of this kind. The Cancer Charity of the Middlesex Hospital, London, was founded in 1792, underwent extension in 1900 when a new wing was added, and extension again three years ago when a new block was built in memory of Mr. Barnato. (See Section I.) There is accommodation for 40 patients, and out-patients are also received. The Cancer Hospital, Brompton, London, was founded in 1851, and now contains 102 beds, only a few of which are set aside for incurable cases. In Manchester there is a Cancer Pavilion and Home attached to the Christie Hospital. It was established in 1892, and contains 30 beds. The Royal Cancer Hospital, Glasgow, founded in 1890, and containing 40 beds, completes the list for Great Britain. For a time there was some special provision for cancer patients in the Infirmaries of Dundee and Liverpool, but the grants having been of only a temporary nature, this has now ceased.

The Continent.—On the Continent provisions of the above character are even less satisfactory than in Great Britain. There is a small pavilion, established in 1902, in the Charité, Berlin, with perhaps a dozen beds; in addition there have been established in Berlin three cancer dispensaries. Originally these were combined with the tuberculosis dispensary, but they are now separated. In 1910 as many as 400 persons with tumors or ulcers sought advice, and in 100 cases the diagnosis of cancer was made.

The Samariter Haus in Heidelberg owes its origin to the energy, and in part also to the munificence, of the famous surgeon, Czerny. (See Section I.) It provides about 60 beds for operable cases. In Hamburg special provision for cancer patients has recently been made at the Eppendorfer Hospital, and similar movements are on foot in Cologne, Dresden, and other German towns. In Vienna there has been founded, under the patronage of the Emperor Francis Joseph, a Society for the Erection of Hospitals for Cancer Patients. With this list all that Europe has done or is doing to provide such special accommodation is exhausted.

IN AMERICA

Of the New York City hospitals (Bellevue and Allied Hospitals) only two receive inoperable cancer patients. All patients suffering from advanced or well-recognized cancer are referred to the City Hospital, Blackwell's Island, to the New York Skin and Cancer Hospital, or to the General Memorial Hospital, and, in some instances of patently incurable cancer, to the Almshouse Hospital or to one of the smaller benevolent institutions which receive such patients.

Almshouse Hospital, Blackwell's Island (New York City Home for Aged and Infirm, Department of Public Charities), receives, and takes care of until death, incurable cancer patients, making provision for any number that may be sent in from the other city hospitals. Only indigent persons, naturally, seek refuge in this institution. Routine treatment conducive to cleanliness and comfort is given.

City Hospital, Blackwell's Island (Department of Public Charities), receives cancer patients who are amenable to surgical treatment, those who are considered inoperable being sent to the Almshouse Hospital. None are refused admission. They are placed in the surgical ward, there being no special cancer ward. After operation the patients are cared for until death.

General Memorial Hospital has two cancer wards in which patients are received who are amenable to surgical or some other form of treatment directed toward the cure of the disease. Twenty beds (10 for males and 10 for females) are reserved for incurable cases.

New York Skin and Cancer Hospital has a total capacity of 110 beds. In the department for the care of advanced cases there are beds for 25. There is a need of accommodation for at least 100 such patients. Plans are under consideration for enlarging the hospital to 250 beds.

PRIVATE INSTITUTIONS

A limited number of private institutions have departments for the care of individual cancer patients, but such institutions, of course, are available only for persons of means. Their existence in no way modifies the conditions that exist among the poor.

BENEVOLENT INSTITUTIONS

It is pertinent to note that some of the "homes" and other institutions of a benevolent or semi-benevolent nature whose object is the care of incurable patients, do not receive cancer patients because of the belief that the disease is contagious.

Fordham Home for Incurables, New York City, receives incurable cancer patients, but not free. A charge of $8.00 per week in the wards, and $10.00 per week in private rooms, is made. It has accommodation for only six cancer patients, and there is always a waiting list.

House of Calvary, New York City, is maintained for *women* suffering from incurable cancer. It was established in 1899, under the auspices of the Women of Calvary, an organization of Catholic widows who devote their lives to the care of incurable cancer patients. The first House of Calvary was established in Lyons, France, in 1847. The one in New York is the only one in the English-speaking world. It is supported by voluntary contributions, is absolutely free to the inmates, and is out of debt. It is non-sectarian, receiving members of any creed and any race. Patients are buried by the Society when necessary. It has a capacity of 30, is always filled, and generally has a waiting list.

St. Rose's Free Home for Incurable Cancer, New York City, was for a number of years the only place in the city, barring the Almshouse Hospital, in which indigent, incurable cancer patients could find refuge. It is under the direction of the Dominican Sisters, the Servants of Relief. A new and much larger hospital has recently been erected by this Order. This institution is the city branch of Rosary Hill Home, at Hawthorne, New York, which is under the direction of "Mother Alphonse" (Mrs. Rose Hawthorne Lathrop). Both institutions are free and are supported by voluntary contributions. Patients are admitted without regard to race or creed. If necessary they are given a decent burial.

The institutions of New York City and immediate vicinity have been given as a fair guide to the possibilities for incurable cancer patients throughout the remainder of the United States. There are numerous private and semi-private sanitaria, hospitals, and "homes" for these unfortunates in different cities, but the fact remains that provisions are nowhere adequate for the care of patients afflicted with this disease.

The American Oncologic Hospital, Philadelphia, with a capacity of 20 beds, the Barnard Free Skin and Cancer Hospital, St. Louis, with 75 beds, the Collis P. Huntington Memorial Hospital, Boston, with 26 beds (see Section I), and the Research Hospital, Buffalo, with 10 beds (see Section I), are illustrations of the limited special provision for the care of cancer patients.

"QUACK" CANCER INSTITUTIONS

While legitimate hospitals and benevolent institutions are refusing admission to this most unfortunate class of patients, it is little wonder that they turn, in their distress, to "quacks," who are ever ready to receive those who are able to pay even a moderate amount.

The laws of the various states are such as to foster institutionary quackery of all kinds, and the cancer "specialist" has availed himself of this leniency in the fullest measure. As a consequence, in many parts of the country are to be found institutions for the treatment of cancer by means of pastes, injections, and other non-surgical methods. Such treatment helps to fill the legitimate homes for incurable cancer patients, but at the same time these "specialists" are not averse to providing homes for such unfortunates as can continue to pay the price until the end.

Fortunately, the campaign of education which has been waged against cancer has included a crusade against these blatant quack institutions, and it is to be hoped that the time is not far distant when they will form a part of the past history of the cancer problem.

THE LOT OF THE PATIENT AT HOME

The life of the victim of incurable cancer is a miserable one under the most advantageous circumstances; unless rendered more bearable by proper care and attention it must indeed represent the maximum of misery.

Imagine the discomfort to the patient, as well as to other members of the household, when forced to live out the remainder of life within the narrow confines of a tenement-house home! Imagine the cross which the care of such a patient, no matter how dearly beloved, inflicts upon the busy mother of the family, when her heart is already heavy with its weight of poverty and hardship, and her hands are overburdened with a multiplicity of household duties!

In pronounced cases, with visible ulcerations, and odors that cannot be disguised, the patient must be fed apart from the rest of the family; his clothing must be laundered separately; the ulcerating surfaces must be dressed and the dressings disposed of; while the suffering of the afflicted one must be witnessed alike by the old and the young of the household.

The unwholesome mental and physical atmosphere in which such a family must live inaugurates a vicious circle of mental depression and physical failure which touches, to a greater or less degree, each member, and which fills the patient's days with the shadows of a hopeless night.

No family of limited means should be forced to give, in the home, this care and attention to a loved one afflicted with incurable cancer. No person afflicted with incurable cancer should be left to spend his last days in enforced neglect, or in the comparative comfort which he knows means the discomfort of his family. Ample provision should be made for the proper institutional care of all such unfortunates.

Inasmuch as the provision now made for the care of such patients is inadequate, many persons of fair or competent means, who might avail themselves of the luxury of the services of trained or practical nurses who engage in what is known as "hourly nursing," meet with an unexpected difficulty, in many instances, in the refusal of nurses to care for cancer patients. Many are deterred because of the disagreeable features of the work, and others by a mistaken belief in the contagiousness or infectiousness of the disease.

It has been the aim throughout this volume to avoid anything that might disgust, but this subject cannot be dismissed without pointing out that the special care required after certain operations, for example, where an artificial opening has been made in the intestinal canal, ought to be provided in institutions. Even the educated and wealthy suffer if they attempt to keep themselves clean instead of trusting to trained nurses. It almost amounts to criminal neglect to leave such sufferers in the homes of the poor.

NEED FOR ADEQUATE FACILITIES

Since incurable cases of cancer are not admitted to ordinary hospitals; since they are often ostracized through ignorant prejudice, fall into the hands of quacks, or require attention after certain operative procedures, it is evident that a very strong case can be made out, on humanitarian grounds alone, for better facilities for their care. In view of the foregoing facts, when one has studied the statistics of cancer, as given in Section III, it becomes evident that a large number of persons must die each year without the care and treatment which should be accorded to them. If this applies to New York City and vicinity, it is reasonable to suppose that it applies in greater measure to other parts of the country and, indeed, reference to other countries shows that throughout the civilized world the same neglect obtains.

It is also apparent that none of the facilities which the Department of Public Charities of New York City supplies are adequate to meet the need, inasmuch as there are many cancer patients who, although poor, do not come under the category of "the indigent." It is further apparent that the few places to which the indigent poor can go and spend their remaining days in comparative peace and quiet (other than the Almshouse Hospital) accommodate so few that it is as nothing compared with the number affected. The victim of incurable cancer should not be forced to decide between remaining a burden to family and friends, or going to a hospital or "home" for indigents. There should be ample provision in every community from which this most unfortunate class of patients may make selection.

As there is need of better facilities for the care of patients in all stages of cancer, particularly during the deplorable period when the disease is irremovable, perhaps inoperable, and certainly incurable, so is there a need for better facilities for the care of these unfortunates as they approach the end. It is frightful to contemplate the state of affairs often found in the wards of institutions for the care of cancer patients, where the dying are left in the midst of the living for hours and sometimes, in lingering cases, even for days. The psychic effect upon other patients is distressing in the extreme, and sometimes days pass before the ward is restored to its normal composure. This is not as it should be. As soon as the signs of dissolution become manifest the patient should be removed to a room set apart for the purpose. Here friends, relatives, and religious counselors may remain to the end without having their sacred privacy invaded by the presence of other patients and attendants. Other occupants of the ward are thus spared the harrowing scenes which so often attend the death of cancer victims.

SUMMARY

The investigation of the facilities for the care of cancer patients has served to emphasize, more than anything else has done, the need of some sort of a campaign of education, some more decisive and concerted coöperation with the various charitable institutions and hospitals in searching out and reaching the poor who are afflicted with cancer, in whatever stage. An enormous amount of good could be accomplished if special cancer hospitals, or, failing these, the general hospitals, would send out intelligent and tactful representatives to visit the various benevolent homes, departments of public charities, societies for improving the condition of the poor, and other similar organizations, for the purpose of getting in touch with cancer patients and their families where there is no medical attendance. Such coöperation would be invaluable from a statistical point of view as well as from that of the humanitarian.

Moreover, such an investigation would serve the further purpose of emphasizing the importance of early and accurate diagnosis, with reference, not only to the presence of malignancy, but to the stage of development of the disease. It is always to be borne in mind that many cases of cancer are pronounced inoperable and hence incurable when they may be both operable and curable. One should be loath, therefore, to consign a patient to the category of the inoperable and incurable until every expedient known to modern medical science as applied to the diagnosis and treatment of malignant disease has been employed.

SECTION XIV

THE CAMPAIGN OF EDUCATION CONCERNING CANCER

INTRODUCTORY REMARKS

Campaigns of education have played a conspicuous part in the development of practically every great movement which has had for its purpose the betterment of living conditions, the eradication of sources of contamination leading to disease, and the maintenance of the health of the individual and of the population as a whole. In some countries, and in certain instances in all countries, the dissemination of knowledge along these lines has been so gradual and so unobtrusive that it may hardly be called a campaign. The history of medicine is marked by instances of this character, the most notable of which, perhaps, relate to vaccination for smallpox, to the control of yellow fever, and to the crusades against malarial and typhoid fever.

In other instances definite campaigns of education have been inaugurated and vigorously carried on, the most notable being those directed against tuberculosis, to a lesser extent against venereal diseases, and, lately, against cancer.

While the apparent increase in the number of those afflicted with malignant disease is creating a public interest which is being fanned into hysteria by sensational newspaper accounts of notable cases and possible "cures," there come urgent calls, from laymen as well as from members of the medical profession, for a more definite crusade, a more vigorous campaign of education, against cancer.

When it is noted—to quote only two of the many recent utterances on the subject—that an important body of public-spirited citizens, in an earnest desire to be helpful, advocates the publication of a "cancer primer" for use in the schools; and that a prominent surgeon, before a general lay audience, calls for the removal by the knife, within twenty-four hours after its discovery, of every lump in a woman's breast—it becomes evident that the campaign of education concerning cancer must be continued with discretion. It must be conducted on a basis entirely different from that on which the fight against tuberculosis is waged.

In the case of tuberculosis, the essential cause—the tubercle bacillus—and the predisposing causes—inherited tendency, lowered vitality, and unsanitary surroundings—are established; the infectiousness of the disease is generally conceded, and the cure, when a cure is possible, is understood.

The situation with regard to cancer is entirely different. The essential cause is not yet discovered, the predisposing causes are matters subject to widely different opinions, and the cure, by other means than by surgical removal of the local manifestations of the disease, is by no means determined.

It scarcely need be pointed out, therefore, that if such a campaign is not cautiously guarded and wisely conducted, with a grasp of all sides of the cancer problem, there is danger of far-reaching harm. The public, tossed from pillar to post, so to speak, by differing medical opinions, will be inclined to discredit the profession and to ignore its warnings. There will then arise a tendency to settle back into hopeless inertia, or to fall into a state of morbid introspection or hysterical watching for danger signals, with resulting physical and mental unrest which may prove a predisposing factor in the initiation of the very disease the dissemination of knowledge is intended to eradicate.

Before a campaign of education concerning cancer can be effectively inaugurated and successfully conducted it is necessary to determine what is actually known to-day about the disease; what may, with expediency, be imparted to the general public; and through what channels such information may best be conveyed.

It will thus be seen that the plan of a campaign is of necessity complex, involving, first, the education of the medical profession, and, second, the education of the public—not the reverse.

In England, at the time of going to press, the question of such education is still being debated. The health committees of some municipalities appear inclined to inaugurate a plan of educating the public by means of lectures to nurses, midwives, and all who are interested in social and hygienic work. It is still doubtful whether any organized campaign will be undertaken along these lines. The sporadic efforts in this direction have not been in progress long enough to permit of an opinion as to their possible utility.

In 1913 the London Cancer Hospital arranged courses of post-graduate lectures similar to those of the New York Skin and Cancer Hospital. The vigorous and lucid campaign conducted in England by the late Sir Henry Butlin concerning the early diagnosis of cancer has not yet found an imitator. Without official sanction, and, indeed, without official enforcement throughout the country, it does not seem that an organized plan of education of the public is likely to succeed, since efforts to obtain compulsory notification have not been supported by the government.

The situation in England resembles that in France, where division of opinion on the part of the authorities has as yet prevented any action being taken.

THE EDUCATION OF THE MEDICAL PROFESSION

Modern medicine is so far-reaching and comprehensive in its scope that it is manifestly impossible for each man and woman upon whom the degree of doctor of medicine is conferred to be expert in the diagnosis of cancer, either by microscopical study or clinical examination. Yet, in a large proportion of cases, it is the general practitioner, the dermatologist, the gynecologist, or the specialist in any field, who is first consulted, and who has, therefore, the first opportunity to diagnose malignant disease, while the surgeon is the court of last appeal, being resorted to only too often, when the case is hopeless.

This being the case, the surgeon, who sees so much of the ultimate outcome of cancer, feels most keenly the paramount importance of early and correct diagnosis and of the prompt institution of the proper treatment. It is inevitable, too, that the surgeon should attribute much of the responsibility for the lack of correct diagnosis and proper treatment to those who are first consulted.

It is evident, then, that the campaign of education must be initiated within the medical profession. The general physician, the specialist in every branch of medicine, and the dentist as well, must be trained to recognize and to guard against precancerous and early cancerous conditions. Just so long as the family physician says to a female patient, particularly one who is passing through the so-called "cancer age," who has a small lump in the breast, subject, perhaps, to irritation by the corset: "Leave it alone! It is nothing unless it pains you; stop thinking about it!" or, to a male patient who has an elevated birthmark, so situated that it is rubbed, perhaps, by a hat-band or suspender buckle: "This is nothing but a birth-mark, how could it hurt you? Come to see me when you have something the matter with you"—just so long is there real and vital need of a campaign of education against cancer among physicians. There is need that they should be taught either to treat such conditions in accordance with the accepted facts concerning the disease, or to refer such patients at once to surgeons or specialists of wider experience.

In this connection it is wise to impress upon the rank and file of the profession certain broad facts which are seemingly fundamental:

(1) That with the increase in the number of cases of cancer reported all over the world, and with the wider interest concerning the disease, all physicians must meet an increased responsibility.

(2) That this increased responsibility, of necessity, demands increased knowledge.

(3) That increased responsibility and increased knowledge call for the highest ethical standard on the part of the medical profession in its management of cases in which the cancer problem is involved, making it incumbent upon the physician or surgeon to treat each case according to the best interest of the patient—to operate when necessary, and to refrain from operating when that course seems desirable.

(4) That this increased responsibility calls for a union of the medical profession upon the essential questions concerning cancer; the adjustment of differences of opinion among themselves; and the discussion in public of only those phases of the subject which may tend to promote early diagnosis and prompt surgical treatment.

If every practitioner of medicine, in any of its branches, were familiar with the predisposing factors in the production of cancer, able to note all the conditions which come under the head of precancerous, and qualified to give wise advice and proper instruction, in accord with the most recent discoveries, rapid strides would be made toward the eradication of at least some of the common forms of the disease.

In Section IV, Chapter 2, the predisposing causes of cancer are discussed, and in Section VIII the subject of prevention by proper attention to these is considered. The etiologic significance of the various predisposing factors is now sufficiently well established for it to be obligatory upon all who assume the responsibility of caring for cancer patients to be familiar with them, and to inaugurate treatment in accordance with such knowledge.

With the establishment of cancer hospitals, and cancer departments in connection with general hospitals, and with the fact that more patients are being operated upon during the earlier stages of the disease than was formerly the case, it is emphatically the duty of the men connected with these institutions, through lectures, clinical demonstrations, etc., to disseminate knowledge among those who form the body of the profession. Thus the standard of diagnosis may be raised so that the family physician, the specialist in other lines, and the dentist will be on guard against the small beginnings. They will then coöperate with the surgeon, and together they will be able to forestall many of the disastrous endings to which neglect or mistakes in diagnosis so often lead.

With this end in view, for a number of years, the New York Skin and Cancer Hospital has conducted two operative clinics each week, and one or more annual lectures have been given, with the presentation of patients, specimens, and other illustrations of the different phases of actual work. Reports of this educational work have been made from time to time, and thus thousands of physicians, from all parts of the country, have been helped by an extensive practical experience, which in this hospital embraces every phase of malignant disease, from the benign, precancerous wart or mole, to the most extensive, irremovable, and inoperable manifestation of cancer. Not only by means of patients who represent the different stages of the disease, but with stereopticon pictures, wax casts, and various other illustrative material, both the negative and positive sides of the subject, from the point of view of diagnosis, have been emphasized.

While the careless and possibly uninformed attitude of the physician is not as common now as formerly, it is still found all too frequently, and has helped materially to swell the enrollment of patients in cancer hospitals and homes for the incurable. On the other hand, since the inauguration of the campaign of education on the subject, there is a growing need of care lest the pendulum swing too far in the other direction—lest "radical removal" may be the advice as freely and thoughtlessly given as was formerly the case with "Let it alone!"

This tendency to rush to extremes is a telling argument in support of conducting the campaign of education against cancer first among the medical profession. The importance of studying cases should be emphasized, and the discussion of theoretical questions left to investigators who are learned in the technicalities of biology and pathology.

A few cases that have recently come under my notice are illustrative of these points. In brief outline their histories are given below.

CASE I.—A young married woman, 33 years old, with two children, the youngest six and a half years of age, recently noticed a little milk in the left breast. Having previously undergone an operation for the removal of a small adenosarcoma from the right breast, she became alarmed about the condition in the other. The family physician was consulted. He assured her that the breast should be removed at once. The condition was due to slight inflammation, with temporary glandular activity, at the time of menstruation, and promptly subsided without treatment. Had she taken the physician's advice, based upon an error in diagnosis, unnecessary mutilation would have resulted.

CASE II.—A married woman, forty years old, with no children, was advised by the family physician to have the entire breast and the axillary glands removed for a small tumor which was obviously a lipoma. The patient was told she had advanced cancer. The small fatty tumor was removed and the diagnosis, substantiated by microscopic examination, proved the fallacy of the advice first given.

CASE III.—A physician's sister, 35 years of age, unmarried, with some of the classical symptoms of chronic intestinal stasis, had a lumpy condition in the breast. She had been reading about cancer, and, upon the advice of two physicians, decided to have the breast removed. I advised against operation, urging general treatment, but the patient went elsewhere and was operated upon. The microscope showed no malignancy. The condition, which was doubtless due to the chronic intestinal stasis, would in all probability have disappeared under treatment for the stasis. Had she taken such treatment she probably would have been less of a nervous invalid than she is today, and certainly would not be the mutilated individual she now is.

CASE IV.—A single woman, 32 years of age, who had been suffering from sciatica, noticed a very small lump in the left breast. She was advised by the family physician to have the breast removed without any delay, for what he pronounced undoubted advanced cancer. Upon examination I found bilateral retraction of the nipple, which was congenital, according to the history. This was not discovered by the physician, who did not make a bilateral examination. Under anti-rheumatic treatment the condition cleared up promptly, except for the retraction of the nipple.

CASE V.—A woman, 63 years of age. Left breast had been removed for cancer fifteen years earlier. I removed the right breast for very early cancer five years ago. Three years ago she returned, complaining of tender spots over the ribs on the right side. Upon examination small nodules were found, closely adherent to the ribs of the right side, and a few on the left side, which had been pronounced advanced recurrent cancer. A few days of anti-rheumatic treatment cleared up the spots of tenderness and the nodules. The patient has had no further trouble, but must be careful with reference to gout and rheumatism.

Case VI.—A single woman, of middle age, consulted me on account of a tumor, of considerable size, in the left breast. There was some retraction of the nipple. The condition had been diagnosed as advanced cancer, and she had been advised to have the breast removed. Suspecting syphilis a blood test was made and proved positive. The tumor disappeared completely under proper medical treatment.

Case VII.—A single woman, 34 years of age, was told that she had advanced cancer of the right breast, which was beyond operation. Upon examination the following conditions were found: A tumor about the size of a small orange in the right breast; an inflammatory area around the nipple; a small discharging sinus within this area of inflammation; some swelling of the axillary glands. It was a typical case of tuberculous sinus of the breast. A few days with local antiseptic treatment applied to the breast caused the disappearance of the swelling in the axilla. The breast was removed, and pathological examination showed no evidence of cancer. The patient has remained well for some years, with freedom from the thought of cancer.

Case VIII.—A woman, 28 years of age, married, with one child, consulted me recently for subdeltoid bursitis. The typical history of chronic intestinal stasis of long duration was elicited—marked and obstinate constipation, abdominal pain, headache, loss of appetite, loss of weight, acrid perspiration, cold and clammy hands, etc. A nodular, more or less painful, condition in both breasts was found in the upper and outer quadrant, which had been pronounced cancer by several physicians. Suspecting that the condition in the breasts was a manifestation of stasis, I put the patient upon large doses of Russian mineral oil, and a dietary and hygienic régime, with the result that the symptoms, including the painful and lumpy condition, were markedly improved. I have seen a number of similar cases in my own practice and in the wards of Guy's Hospital, London, service of Sir W. Arbuthnot Lane.

In numbers of instances menstrual lumps in the breast have been mistaken for cancer.

Such cases emphasize one side of the question of mistaken diagnosis. Every case of advanced cancer of the breast may be said to emphasize the other side, which leads to neglect or delay. All cases, whether the mistake in diagnosis be positive or negative as regards cancer, emphasize the importance of a unification of knowledge concerning the known facts in relation to malignant disease.

It should be impressed upon the body of the medical profession that, as a rule, they should entrust the experimental investigation of cancer to reliable research institutions, where all theories, whether of cause or cure, are studied on a scientific basis, without danger to the victims of the disease. In exceptional instances, men and women with excellent medical training, but with no institutional affiliations, may work independently, and their efforts should be encouraged. On the other hand, unscrupulous or overconfident physicians, working independently, may do incalculable harm, for example, by testing their theories of treatment upon trusting patients until it is too late for surgical intervention, and consequently too late for cure.

It is no uncommon occurrence for physicians to appeal to the New York Skin and Cancer Hospital, and doubtless other similar institutions have a like experience, for "cancer material" with which to make a "serum" or "vaccine" or other "cure," in accordance with some new theory of treatment. Some of these applicants, who are not prompted by high or sincere motives, have been known to boast of their "researches," thus wilfully playing upon the ignorance or credulity of their patients, while at the same time they enrich themselves. The patient, meanwhile, may be richer in experience but poorer in money, and is often bankrupt as far as his chances for recovery are concerned. The eradication of this kind of "research" should be a part of the work of education.

THE EDUCATION OF THE PUBLIC

NEED THE LAYMAN BE INSTRUCTED?

The need for the enlightenment of the laity concerning cancer is twofold: (1) For the establishment of a spirit of confidence in, and of willingness to coöperate with, the medical profession in the prevention of cancer by intelligent attention to the general health and to the special conditions which predispose to the development of the disease, as outlined in Section IV, Chapter 2 (*Predisposing Causes*), and Section VIII (*Prophylaxis*). (2) For the development of keener discrimination in the selection of a physician or surgeon. The public should be sufficiently instructed concerning the ethical principles which govern the conduct of the recognized body of the medical profession to be able to differentiate between the capable and conscientious practitioner and the "quack" who, solely by virtue of a medical license, has power to attract and to delude the suffering.

Unfortunately, in no country to-day is the medical law so constituted and so administered as to entirely eliminate the unscrupulous practitioner and the "quack." Even the most intelligent members of the non-medical part of a community may be deceived by such members of the profession. Interesting illustrations of this are cited in Section IX, *The Investigation of "Cancer Cures."*

The imminence and extent of the danger from quackery are greater than is generally realized. The advertisements of men who may be rightly classed as cancer quacks are published in glaring type in an alluring phraseology in many of the leading periodicals, both secular and religious. So far, in most states and countries, medical laws have proved inadequate for the suppression of this practice. Even for communications such as those referred to by Paget, in the following letter, there seems no adequate redress. Unfortunately, there is always danger that many such statements as those to which he directs attention may go without contradiction, or that, when published, such contradiction may not reach the readers who may have been influenced by the assertions contradicted.

"CANCER AND ANTI-VIVISECTION."

"To the Editor of the Daily Mail."

"Sir:—A new anti-vivisection magazine has lately appeared; it is called the *Journal of the Society for the Prevention and Relief of Cancer.* It contains half a page of sentences quoted from another magazine, called the *Health Record.* These sentences are adverse to the treatment of cancer by operation; and they are put as quotations from Sir Benjamin Brodie, Professor Syme, Sir James Paget, and others.

"Brodie died fifty-one years ago, and Syme forty-three years ago. Statements made more than half a century back, when the conditions and methods of surgery were very different from what they are now, ought not to be quoted without dates put to them. Neither are any references given. Without dates and references, we cannot be sure that these statements were ever made. But we can be quite sure that neither

Brodie, Syme nor Paget, were they living now, would dream of saying anything of the kind. They would condemn with unsparing anger the use which has been made of their names.

"(Signed) STEPHEN PAGET.
Hon. Secretary Research Defense Society,
21, Ladbroke Square, W., London."

It often happens that literature, such as that denounced above, emanates from persons holding medical degrees, whose writings, therefore, are very dangerous. A medical man is privileged to hold any opinion he chooses concerning the nature, cause, treatment, or even the cure of cancer or any other disease, provided that he holds his views honestly. But it is a different matter when statements in the public press are clothed in the catch phraseology of avowed quacks, and when the appeal is made to a low order of intelligence and not to educated medical opinion. Moreover, unreliability is always evident when cases given by way of illustration of the claims made, are incapable of independent verification. Much literature of this character has been published which is but veiled advertisement of the author's claims to be a "cancer expert."

The average layman, who looks upon the question of medical ethics from the business point of view, sees nothing amiss in the fact that Dr. So-and-So advertises to cure cancer. The extravagant claims of the complete eradication of cancer—"roots and all"—without the use of the surgeon's knife, appeal to many victims of the disease. The advertising doctor is taken on faith—and eventually the patient comes, often without money, without hope, and with not the slightest chance of cure, to the cancer hospital.

The public needs, therefore, to be taught the difference between the man who, independently, and without the sanction of the medical profession, advertises to "cure" cancer, and the skilled, conscientious, and recognized members of the profession who are carefully safeguarding the patient while diligently striving to solve the cancer problem. Much excellent educational work along this line has already been accomplished by secular journals, medical journals, medical societies, and by popular lectures, etc., but much remains yet to be done.

HOW BEST TO CONDUCT THE CAMPAIGN OF EDUCATION?

The above is still a mooted question. Among other experiments along this line, for a number of years, Winter, Pinkus, and von Duehrrsen have been sending broadcast throughout

Germany circulars of information and instruction for women, with especial reference to cancer of the pelvic organs. They have also caused similar matter to be published in the secular press at stated intervals. At first it was reported that, as a consequence of this form of enlightenment, the number of women who presented themselves at the clinics of these surgeons while yet in the early and curable stages of such cancers, increased year by year. Later accounts do not substantiate the first reports as regards the number of women directly presenting themselves, although it appears that much good has resulted from the instructions issued to midwives.

In this connection it is interesting to note the following statement from H. J. Boldt,[1] Professor of Gynecology, of the New York Post-Graduate Medical School and Hospital, who has recently made a study of the practical application of this plan of publicity. "During the past summer," he says, "I had an opportunity to converse with a number of men who are connected with university hospitals and who have studied carefully the question of publicity. Those to whom I put the question assured me that they did not find any advantageous result. They had seen no larger percentage of operable cases since the 'Winter' circular letters had been sent out, and since the lay press had published articles written by Winter on the subject of uterine cancer. What they had observed, following the general publicity in the lay press, was that 'a goodly number of neurasthenic women were made more nervous and consulted physicians in fear of cancer.'"

"It is my opinion," continues Boldt, "strengthened by this information obtained abroad, that we are not likely to get under observation a larger percentage of incipient cases of cancer of the uterus by giving the cancer symptoms to the public through the medium of the lay press. On the contrary, it is more than likely that, of the large number of women suffering from leukorrhea, those of the neurasthenic type will simply acquire an aggravation of their nervousness, with this result: They will rush to physicians for examination, and, if told they have no malignant disease, will be distrustful, and seek the advice of others. I am convinced, therefore, that the better way—the only rational way, indeed—is to impress on the profession the grave importance of being conscientious in the matter of examination, and never superficial."

[1] Boldt, H. J.—"How May We Reduce the Mortality from Cancer of the Uterus? With Special Reference to Treatment and to Publicity Through the Lay Press," *Jour. Am. Med. Assn.*, Vol. LX, March 29, 1913, pp. 968-972.

Many physicians are of the opinion that all teaching on the subject of cancer should emanate from the family physician. If all homes were at all times in touch with a family physician sufficiently trained in diagnosis to be able to recognize the early symptoms of cancer, or to give proper instruction concerning it, this plan would be all-sufficient as a scheme for cancer education. But at present such is not the case.

When once the medical profession has determined upon a strictly practical fund of information; when doctors agree to confine theoretical matters to their own society meetings, leaving all unsettled questions out of public discussion, whether in lectures or articles for publication, then the campaign of education may be conducted upon a rational and useful basis. Many aids may then be utilized for the dissemination of knowledge, such as Young Men's and Young Women's Christian Associations, Clubs of Trained Nurses, or Women's Clubs of any kind. These and other similar organizations may become avenues for spreading information.

The most important step in this entire plan, however, is the education of the public to the point of undergoing periodical examination, not specifically with reference to this or that condition, but for a general inspection. If the physician is educated to make such an investigation seriously, and if the patient is taught to consider this as the rational method to be pursued in health maintenance, a long stride will have been taken toward the prevention of many other ills, as well as of much of the suffering which invariably ensues if the stage of irremovable cancer is reached.

Extensive business enterprises and successful commercial houses to-day pay large salaries to "efficiency men." These are experts who keep watch of the general workings of the business, advising as to the betterment of methods or the avoidance of difficulties. They are often most needed when those directly interested are absorbed by what appears to be a successful rush, and are blind to conditions which spell ultimate disaster. Hundreds of thousands of dollars are saved yearly by the employment of such experts.

Fine machinery, notably the automobile, if the best service is to be had from it, is constantly subjected to careful inspection. The human machine is far finer and infinitely more delicate; it is constantly subjected to immensely greater strain; yet how few give to it any proportion of the care bestowed upon a motor car.

The teeth and the eyes are practically the only parts of the anatomy that receive adequate and regular attention. The majority of people consult the dentist and the oculist with a commendable degree of system and regularity. But similar attention is not yet paid to the well-being of the body as a whole. Efficiency physicians are needed to point out wrong methods of living, to warn when a downward path is taken. Often when the body is seemingly strong and well and under "full steam" so to speak, a watchful and intelligent eye will foresee danger to which the person absorbed in the pressure of living is blind.

Pending the time when such conditions shall be brought to pass, it seems best that the campaign of education against cancer should take note of the following facts, and disseminate knowledge along the lines indicated.

(1) That the hereditary and congenital acquirement of cancer are subjects which require much more study before any definite conclusions can be formed concerning them, and that, in the light of our present knowledge, they hold no special element of alarm.

(2) That the contagiousness or infectiousness of cancer is far from proved, the evidence to support this theory being so incomplete and inconclusive that the public need have no concern regarding it.

(3) That the public need merely be instructed to apply to cancer the same precautionary measures that should be brought to bear in the care of any ulcer or open wound.

(4) That the danger of the accidental acquirement of cancer is far less than that from typhoid fever, syphilis, or tuberculosis.

(5) That in the care of cancer patients there is much less danger to the attendant from any possible acquirement of cancer than there is of septic infection, or blood poisoning from pus organisms.

(6) That the communication of cancer from man to man is so rare, if it really occurs at all, that it may be practically disregarded.

(7) That in cancer, as in all other disease, attention to diet, exercise, and proper hygienic surroundings is of the utmost importance.

(8) That cancer is local in its beginning.

(9) That, when accessible, it may, in its incipiency, be removed so perfectly by radical operation that the chances are overwhelmingly in favor of its non-recurrence.

(10) That, when once it has advanced beyond the stage of cure, suffering in many cases may be palliated and life prolonged by surgical means.

(11) That while other methods of treatment may, in some cases, offer hope for the cancer victim, the evidence is conclusive that surgery, for operable cases, affords the surest means of cure.

(12) That the diminution of the risk of cancer by the eradication of known predisposing causes, or at least of causes which, from long and varied experience, have come to be accepted as known, seems to be possible.

(13) That prominent among these predisposing factors, for which one should be on guard, are: general lowered nutrition; chronic irritation and inflammation; repeated acute trauma; cicatricial tissue, such as lupus and other scars, and burns; benign tumors—warts, moles, nevi (birth-marks), etc.

(14) That certain occupations, notably working in pitch, tar, paraffin, or anilin, and with X-rays, if not safeguarded, are conducive to the production of cancer, presumably on account of the chronic irritation or inflammation caused.

SUMMARY

The campaign of education concerning cancer, to be rational and safe, must be made to apply first to the general body of the medical profession, and, through the profession, to the public at large. It must have for one of its objects the maintenance, upon the part of the physician, of a standard of ethics which insures the best interest of the patient, regardless of operative and mortality statistics; and the development, upon the part of the patient, of a spirit of confidence in and coöperation with the physician. It should be aimed at health rather than disease; at physiology rather than at pathology. It must be directed toward the prevention of cancer by the maintenance of the general health, as well as toward the eradication of the various factors, within and without the body, which are thought to exercise a predisposing influence in the initiation of malignant disease.

Such a campaign, intelligently inaugurated and vigorously waged, would undoubtedly tend:

(1) To decrease the number of those primarily affected with cancer, by modifying or eliminating predisposing and precancerous conditions.

(2) To forestall, in large measure, the danger of recurrent manifestations because of an awakening to the importance of early and radical removal of the primary lesion.

(3) To lower the mortality figures, by intelligent attention to precancerous conditions and early cancerous affections.

THE OUTLOOK

The great advance in knowledge concerning cancer made during recent years involves the elimination of a number of theories of the etiology of the disease.

Cancer is no longer to be considered merely as the development of embryonic "rests" stimulated to unfold their latent powers of growth.

There are stronger reasons now than ever before for abandoning the theory that cancer is a disease which is directly communicable by infection, and no indisputable evidence has been offered to prove that it is transmitted by an intermediate host.

Much new evidence has been advanced as to the causative influence of chronic irritation in some forms of cancer. A possible explanation of the disease has been found in the variations to which cells are liable in the direction of losing their normal differentiation, and, more rarely, of acquiring powers of continued growth.

There is urgent need to determine whether Ehrlich is right in assuming a peculiar form of immunity—"atreptic immunity"—because of the etiological application made of it. According to this view, circumscribed groups of cells grow into tumors because their appetite for taking up food is greater than that of the rest of the body.

It is equally necessary to determine whether the workers of the Imperial Cancer Research Fund are right in denying the existence of atreptic immunity, their conclusions, likewise, having important etiological bearings in that they appear to have revealed the fact that continuous growth results as a consequence of a loss of power of cells to control their own growth, or to call forth resistance to growth. This point is of the utmost importance, since its firm establishment would eliminate the whole group of etiological and working hypotheses which seek for the cause of cancer in stimulus to development.

The whole trend of investigation points not to a single cause, but to a number of causes of cancer. There is reason, too, for the belief that the disease to which the term cancer is applied is still a composite, despite the fact that syphilis, tuberculosis, actinomycosis, blastomycetes, and even leprosy, which were formerly confused with cancer, are now known to be separate entities, each with its specific cause. Who can tell to what further extent this process of differentiation and isolation may lead? The time may come when carcinoma and sarcoma will be separated into diseases undeniably distinct one from the other.

While this complexity of etiology remains unsolved, the prevention of cancer cannot become a truly practical problem, and the only methods which can be recommended with reasonable likelihood of diminishing the prevalence of cancer are measures which have for their purpose the elimination or avoidance of all forms of chronic irritation.

From the moment it was recognized that chronic irritation and acute trauma may induce cancer, it was inevitable that a large field for dispute would be opened in connection with accidental injuries, negligent litigation, workingmen's compensation acts and insurance, and similar matters. Whether injury has or has not caused cancer in a given case is, of course, primarily a medical and not a legal question. Yet, inasmuch as a secondary legal aspect may arise, both science and common sense require that rational criteria be fixed for determining whether a cancerous condition has been caused or induced or superinduced by an earlier irritation, by trauma, or by other injury. The elucidation of this phase of the problem furnishes, therefore, an important field of research for the future.

Pending the time when the cause or causes of cancer shall have been discovered, and when it will be possible to cure the disease by other means than by surgical removal, what is the outlook for the cancer problem and the cancer patient? In the light of modern cancer research is the prospect for the solution of the problem a hopeful one? Are we justified in encouraging the belief that the outlook for the patient is less despairing than formerly?

The study of the various phases of the cancer problem which are outlined in the preceding pages must convince everyone that the concentrated effort of so many earnest and intelligent investigators is slowly but surely clearing away much of the mystery which for centuries has obscured the questions of the initiation and the progress of the disease.

With the careful clinical and laboratory examinations to which we now know all patients should be subjected when they present themselves for treatment, there is justification for the belief that in future a progressively smaller and smaller proportion of cases of cancer will be wrongly diagnosed, and consequently wrongly treated.

With the campaign of education directed against the neglect of the many small things which may lead to the graver condition known as cancer; with the increasing mastery of the predisposing causes of the disease, and with the greater willingness on the part of individual patients to present themselves for surgical treatment for its early manifestations, there is hope that the future will be marked by a progressive decrease in the number of persons who come within the category of those having inoperable and irremovable cancer.

With the perfection of surgical technic which characterizes modern practice, and with the intelligent utilization of the various adjuvant methods and measures which may be employed to alleviate suffering, the lot of those who are no longer amenable to surgical cure is certainly far less miserable and hopeless than was that of persons similarly afflicted even a decade or two ago.

While it cannot be gainsaid that the cancer problem to-day is still fraught with perplexity and uncertainty, one indisputable fact stands out in bold relief, serving as both guide-post and danger-signal for the present and the future—*If cancer cells be cut out soon enough a permanent cure is effected!* This alone is sufficient to warrant the statement that we are "travelling hopefully!"

GENERAL BIBLIOGRAPHY

No attempt is made to give a complete bibliography of any subject in the table of contents. The literature of cancer is so voluminous that it is neither available nor dependable in its entirety. For this reason it has seemed expedient to correlate a selected list of contributions concerning the different phases of the cancer problem, and to cite articles and volumes which contain full and valuable lists of references.

Inasmuch as certain subjects overlap, to a greater or less extent, referances concerning these are given without differentiation. Other subjects are individually considered.

References under each subdivision are arranged in alphabetical sequence of authors' names.

HISTORY

(1) Ancient
(2) Modern Cancer Research

Albert, Aaron.—DE DIAGNOSI MORBORUM MAMMÆ. Gryphiæ, F. G. Kunike, 1857.

Alberts, J. E.—"Over Kanker. Historisch-critisch en experimental Onderzook." Gröningen, 1885.

Alberts, J. E.—"Das Carcinom in historischer und experimentell-pathologischer Beziehung." Jena, 1887.

Annis, E. J.—"Cancer; A Brief History, with some Remarks on the Prophylaxis of Cancer of the Digestive Organs," *Am. Jour. of Gastro-Enterology,* 1911-1912, i, p. 1.

Barduzzi.—Sui Codicici e sulle edizione del libro "De re Medica" di Aulo Cornelio Celso: Riv. di storia crit. d. sc. Med. e Nat. Faenza, 1910, i, 11-13.

Bashford, E. F.—Verhandlung des Komitees für Krebsforschung, Hft. iii, 1903-4, reprinted from *Deut. med. Woch.,* 1904; First Annual Report, Imperial Cancer Research Fund, 1903; Second Scientific Report, Imperial Cancer Research Fund, Part I, 1905, etc.

Bashford, E. F.—"The Obligation Imposed on the General Practitioner by the Development of the Experimental Investigation of Cancer." *The Practitioner,* 1911, Vol. LXXVI, p. 337.

Baudouin.—"La dernière maladie de Napoléon I," Gaz. méd. de Paris, Mar. 18, 1901.

"Cancer Cures in the 18th Century," *Brit. Med. Jour.,* 1905, ii, p. 56.

Coupland, Sidney.—The Cancer Charity of the Middlesex Hospital, 1792-1902, Reports from the Cancer Research Laboratories of the Middlesex Hospital, Vol. I, London, 1902, p. 1.

Editorial, *Brit. Med. Jour.,* October 22, 1910, p. 1266.

Editorial, *The Practitioner,* April, 1899, p. 362.

Ewing, James.—"The Cancer Research Hospital." *New York Med. Jour.*, December 27, 1913, p. 1241.

Justamond, J. O.—"An Account of the Methods Pursued in the Treatment of Cancerous and Scirrhous Disorders and Other Indurations," 1870.

Klein.—"Zur Geschichte des Krebses," *Arch. f. phys-diatet. Therapie*, Berl., 1904, vi, 44-74.

Landau, R.—"Die ältesten medizinischen Drucke; eine bibliographische Studie," *Mitt. z. Geschich. d. Med. u. d. Naturw.*, Hamb. u. Leipz., 1904, iii, 246-259.

Ledoux-Lebard, R.—"Documents pour servir à l'étude du charlatanisme du cancer au XVIIIème siècle," *Bull. de l'assoc. franç. pour. l'étude du cancer*, Paris, 1911, iv, 383-413.

Licht, H.—"Ueber Geschichte und Entwicklungsgeschichte des Carcinoms," Würzburg, 1891.

Mackenzie, Sir Morell.—"The Fatal Illness of Frederick the Noble," London, 1888.

Mamlock, G. L.—"Krebsforschung im Zeitalter der Aufklärung," *Zschr. f. klin. Med.*, 1904, lii, p. 178.

Menétrier, P.—"Cancer," Paris, 1908.

Meunier.—"Cœlius Aurelianus; maladies aiguès et maladies chroniques; le méthodisme," Janus, Harlem, 1906, xl, 129.

Meunier, L.—"Histoire de la Médecine Depuis ses origines jusqu' à nos jours. Préface par le Professeur Gilbert Ballet, President de la Soc. franç. d'Histoire de la Médecine." Paris. 1911.

Mitchell, R.—"A General and Historical Treatise on Cancer Life; Its Causes, Progress, and Treatment," London, 1879.

Muir, John.—"The Cancer Curer in South Africa," *South Africa Medical Record*, Jan. 25, 1906, p. 5.

Mumford, James G.—"Studies in Cancer—Historical and Critical," *Annals of Surgery*, January, 1909.

Orth, J.—"Ueber die Krebsgeschwulst des Menschen," Berlin, 1909. G. Reimer, p. 107-125.

Paget, Sir James.—"Lectures on Surgical Pathology," London, 1853.

Paget, Sir James.—The Morton Lecture on Cancer and Cancerous Diseases. *Lancet*, November 19, 1887.

Park, Roswell.—"A Further Inquiry into the Frequency and Nature of Cancer," *The Practitioner*, 1899, Vol. LXII, April, p. 385.

Pemberton, O.—"Observations on the History, Pathology, and Treatment of Cancerous Diseases," London, 1858.

Peyrilhe, B.—"A Dissertation on Cancerous Diseases," Trans. from the Latin, with notes, London, 1771.

Protocol of the Meeting for the Organization of the International Association for Cancer Research—Saturday, May 23, 1908: *Cancer. Internat. Monatschr.*, etc., Berl., 1908-9, 38, 78.

Quadrio, Giuseppe Maria.—"Nuovo methodo por curare ogni canchero coperto e specialmente le ghiande delle Mamelle, e di altre parti del corpo," Venezia, 1750.

Sandwith, F. M.—"A Brief History of Cancer," *The Clin. Jour.*, Lond., 1909-10, xxxv, p. 360.

Sandwith, F. M.—"Two Historical Cases of Cancer, and the Treatment of the Disease," *The Clin. Jour.*, Lond., April 13, 1910.

Sydenham.—"Observations on the History and Cure of Acute Diseases." (Revised, etc., by John Swan, M.D., MDCCXLIX.)

Virchow, Rudolph.—"Die Kranhafte Geschwülste," *Onkologie*, 1863-65.

Vaughan, J. W.—"Some Modern Ideas of Cancer," *Jour. Am. Med. Assn.*, 1910, liv, p. 1510.

Walshe, Walter Hayle.—"The Nature and Treatment of Cancer," London, 1846.

Wolff, Jacob.—"Die Lehre von der Krebskrankheit von den 'ältesten Zeiten bis zur Gegenwart,'" Part I, 1907; Part II, 1911, Jena, 1911.

GENERAL DISTRIBUTION

(1) Botanical
(2) Zoölogical
(3) Geographical and Ethnological—Statistical Considerations—Site-incidence

Botanical

Hecke, L.—"Der 'Krebs' der Pflanzen," *Wien. klin. Woch.*, 1912, xxv, 229-231.

Hutchinson, J.—"Does Cancer Occur in Vegetables?" *Lancet*, Lond., 1912, i, 756.

Jensen, C. O.—Von Echten Geschwülsten bei Pflanzen. Travaux de la 2ème Conference Internationale pour l'étude du cancer, 1910, Paris, 1911, p. 243.

Noël, L.—Sur la topographie et la contagion du cancer, *Rev. des maladies cancéreuses*, Paris, 1896-1897, ii, pp. 137, 201; also Thèse de Paris, 1897.

Packard, Horace.—"Tree Cancer. A Striking Analogy between Certain Vegetable Tumors and Malignant Animal Tumors," *Boston Med. and Surg. Jour.*, 1911, Vol. CLXV, p. 247.

Penhallow, D. P.—"A Birch Rope. An Account of a Remarkable Tumor Growing upon the White Birch." Trans. Roy. Soc. of Canada, 1906, 2 s. Vol. XII, Pt. I, Sec. 4, pp. 239-255.

Potebnia, A.—"Ein neuer Krebserreger des Apfelbaumes, Phacidiella discolor (Mout et Sacc.) A. Pot., seine Morphologie und Entwicklungsgeschichte," *Ztschr. f. Pflanzenkr.*, Stuttg., 1912, xxii, 129-148. 3 pls.

Smith, E. F.—"The Etiology of Plant Tumors," *Science*, New York, and Lancaster, Pa., 1909, n. s., xxx, 223.

Smith, E. F.—The Structure and Development of Crown-Gall: A Plant Cancer, U. S. Department of Agriculture, Bureau of Plant Industry, Bull. No. 255, June 29, 1912.

Smith, E. F.—"Pflanzenkrebs versus Menschenkrebs," *Centralbl. f. Bakteriol.*, etc., Jena, 1912, xxxiv, 2 Abt., 394-406.

Smith, Erwin F. (U. S. Dept. Agr., Washington, D. C.).—"Cancer in Plants": 17th Int. Cong. of Medicine, London, 1913, Sect. III, Genl. Pathology and Pathol. Anat.—Independent Paper, p. 281.

von Tubeuf, Karl, Freiherr.—"Diseases of Plants induced by cryptogamic parasites: Introduction to the Study of pathogenic Fungi, slime fungi, bacteria, and algæ," English edition by William G. Smith, Lond., 1897.

von Tubeuf, Karl, and Smith, William G.—"'Witches brooms,' due to Æcidium elatinum," Diseases of Plants, 1897, pp. 18, 24, 72, 88, 404, 410.

Vuillemin, P.—"Des tumeurs des plantes comparées aux tumeurs animales," *Biologica*, Par., 1913, iii, 101-109.

Zoölogical

Bashford, E. F.—"The Significance of the Zoölogical Distribution, the Nature of the Mitoses, and the Transmissibility of Cancer," *Brit. Med. Jour.*, Lond., 1904, i, 296-271.

Bashford, E. F.—"The Zoölogical Distribution, the Limitation in the Transmissibility, and the Comparative Histological and Cytological characters of Malignant New Growths," Sci. rep. on the investigations of the Cancer Res. Fund, London, 1904.

Baumgartner, A.—"Ueber einen malignen Tumor mit ausgebreiteter Metastasenbildung bei einen Kaninchen," *Centralbl. f. allg. Path. u. pathol. Anat.*, Jena, 1906, xvii, 769-772.

Beebe, S. P.—"A Study of the So-called Infectious Lymphosarcoma of Dogs," *Jour. Med. Res.*, 1906, n. s. 10, p. 209.

Bland-Sutton.—"Tumours in Animals," *Jour. of Anat. and Physiol.*, 1884-5, Vol. XIX, p. 430.

Bonnet.—"Studien zur Physiologie der Fische," *Bayer. Fischerei-Ztg.*, München, 1883; *ibid.*, 1884.

Brooks, Harlow.—"Concerning the Occurrence of Neoplasms in Wild Animals, with the Report of a Case of Sarcoma of the Ovary in Nyctereutes Albus," *Am. Jour. of Med. Sci.*, May, 1907, Vol. CXXXIII, p. 769.

Burnet, E.—"Contribution à l'étude de l'épitheliome contagieux des oiseaux," *Ann. de l'Inst. Pasteur*, Par., 1906, xx, 742-765. 2 pls.

Calkins, G. N.—"Protozoölogy," 1909.

Collinge, Walter E.—"Note on a Tumor in Anodonta Cygnea, Linn.," *Jour. of Anat. and Physiol.*, 1890-91, xxv, p. 154.

Cornil, V., et Petit, G.—"Quatre nouvelles observations de cancer de la mamelle, chez la chienne et la chatte," Bull. et Mém. Soc. anat. de Paris, 1905, lxxx, 137-143.

Cornil, V., et Petit, G.—"Papillo-épithéliome kystique de la mamelle chez une chienne," Bull. et Mém. Soc. anat. de Paris, 1905, lxxx, 128-131.

Cornil, V., et Petit, G.—Épitheliome à cellules cylindriques de la mamelle generalise au poumon et au foie, chez une chatte," Bull. et Mém. Soc. anat. de Paris, 1906, lxxxi, 208-211.

Cornil, V., et Petit, G.—Énorme chondrosarcom ossifié de la mamelle chez une chienne," Bull. et Mém. Soc. anat. de Paris, 1906, lxxxi, 21-24.

Cornil, V., et Petit, G.—"Sarco-épithéliome végétant de la mamelle chez une chienne," Bull. et Mém. Soc. anat. de Paris, 1906, lxxxi, 218-223.

Clunet, J.—"Le cancer au Maroc," Bull. de l'Assoc. franç. pour l'étude du cancer, Paris, 1913, v. 167.

Eberth, C. J.—"Multiple Adenome der Froschhaut," *Virchow's Arch.*, 1868, Vol. XLIV, p. 12.

Ehrenreich, M.—"Weitere Mittheilungen über das Vorkommen maligne Tumoren bei Hühnern," *Med. Klin.*, Berl., 1907, iii, p. 614.

Ehrenreich, M., und Michaelis, L.—"Ueber Tumoren bei Hühnern," *Ztschr. f. Krebsf.*, 1906, 4, 586.

Field, Eva H.—"A Contribution to the Study of Malignant Growths in the Lower Animals," *Jour. Am. Med. Assn.*, 1894, Vol. XXIII, p. 982.

Fiebiger, J.—"Ueber Hautgeschwülste bei Fischen nebst Bemerkungen über die Pockenkrankheit der Karpfen," *Ztschr. f. Krebsf.*, 1908-9, 7, p. 165.

Fiebiger, J.—"Eine Osteochondrosarkom bei einem Karpfen," *Ztschr. f. Krebsf.*, 1908-09, 7, p. 371.

Fiebiger, J.—"Eine Rhabdomyom bei einem Kabljau," *ibid.*, p. 382.

Flemming, W.—"Weitere Beobachtungen über die Entwicklung der Spermatozomen bei Salamandra maculosa," *Arch. f. mikr. Anat.*, Bonn, 1887, xxxi, 71-97, 1 pl.

Fradyean, J. M.—"The Occurrence of Cancer in the Lower Animals," *The Practitioner*, Lond., 1899, Vol. LXII, n. s. ix, p. 456.

Gaylord, H. R.—"An Epidemic of Cancer of the Thyroid in Brook Trout in a Fish Hatchery," *Jour. Am. Med. Assn.*, Jan. 30, 1909, Vol. LII, p. 411; *ibid.*, Jan. 15, 1910, Vol. LIV, p. 227.

Gaylord, Harvey R., and Marsh, Millard C.—"Carcinoma of the Thyroid in the Salmonoid Fishes," The Bulletin of the Bureau of Fisheries, United States Department of Commerce, Vol. XXXII, 1912, Document No. 790. Issued April 22, 1914.

Gilruth.—Reports of the New Zealand Department of Agriculture, 1901-2.

Harrison, A. G.—A Study in the Gardens of the Clifton Zoölogical Society, *Medico-Chir. Jour.*, Bristol, 1894, Vol. XII, p. 285.

Hertwig, R.—"Ueber physiologische Degeneration bei Actinosphärium Eichhornii," *Festschrift f. Haeckel*, 1904.

Jaboulay.—"Poissons atteints de goitres malins héréditaires et contagieux," *Lyon méd.*, 1908, Vol. CX, p. 335; also abstr. in *Jour. de Méd. et Chir.*, 1908, p. 239.

Jaeger, Alfred.—"Die Melanosarkomatose der Schimmelpferde," *Virchow's Arch.*, 1909, 198, Hft. 1, p. 1.

Jaeger, Alfred.—"Über den vollwertigen Organbau eines Talg drusenkarzinoms beim Hund," *Virchow's Arch.*, 1910, 199, p. 95.

Koch, M.—"Geschwülste bei Tieren," *Verhandl. d. deutsch. Gesell. f. Pathol.*, 1904, 136.

Loeb, Leo, and Jobson, George.—"On Carcinoma in Cattle," *Medicine*, April, 1900, p. 286.

Loeb, Leo.—"Ueber den Krebs der Thiere," *Arch für klin. Chir.*, 1903, Bd. LXX, p. 845.

Loeb, Leo.—"Ueber das endemische Vorkommen des Krebes beim Tier," *Centrlbl. für Bakter.*, Bd. XXXVII, 1904.

Ludwig, Eugen.—"Sarkom der Leber mit diffuse Nierensarkomatose bei einem Hahn," *Ztschr. f. Krebsf.*, 1913, 13, p. 81.

Marine, David, and Lenhart, C. H.—"Observations and experiments on the so-called thyroid carcinoma of brook trout (Salvelinus fontinalis) and its relation to ordinary goitre," *Jour. Exper. Med.*, May 1, 1900, p. 311.

Marine, David, and Lenhart, C. H.—"Observations and experiments on the so-called thyroid carcinoma of brook trout (Salvelinus fontinalis) and its relation to ordinary goitre," *Jour. Exper. Med.*, 1910, Vol. XII, p. 311. Under same title a similar issue, Bull. No. 7, Dept. of Fisheries of Penna., Harrisburg.

Marine, David, and Lenhart, C. H.—"On the occurrence of goitre (active thyroid hyperplasia) in fish," *Johns Hopkins Hosp. Bull.*, April, 1910, xxi, p. 95.

Marine, David, and Lenhart, C. H.—"Further observations and experiments on the so-called thyroid carcinoma of the brook trout (Salvelinus fontinalis) and its relation to endemic goitre," *Jour Exper.*

Med., 1911, Vol. XIII, p. 455; also, "Continued observations and experiments on the so-called thyroid carcinoma of brook trout (Salvelinus fontinalis) and its relation to ordinary goitre." Bull. No. 8, May 1, 1911, Dept. of Fisheries of Penna., Harrisburg. (Similar to preceding with the addition of "Practical Suggestions" as Part III.)

Marine, David, and Lenhart, C. H.—"On certain limitations in interpreting thyroid histology," *Johns Hopkins Hosp. Bull.*, July, 1911, Vol. XXII, No. 244, p. 217.

Nichols.—Third Report of Harvard Cancer Commission, 1905, p. 79.

Pettit, A.—"Fibrome observé sur un Mégalobatrachus maximus à la ménagerie du muséum," Bull. Mus. Hist. Natur., Paris, 1902, p. 301.

Pettit, A., et Vaillant, L.—"Lésions stomacales chez un Python de Seba," Bull. Mus. Hist. Natur., Paris, 1902, p. 301.

Petit, G., et Germain, R.—"Des adénomes biliaires et de leur transformation cancéreuse chez les carnivores domestiques," Bull. de l'Assoc. franç pour l'étude du cancer, 1910, 3, 308-318.

Pick, L.—"Zur Frage vom Vorkommen des Carcinoms bei Vögeln: Grosse platten Epithelialkrebs des Mundhöhlenbodens bei einem Huhn," *Berl. klin. Woch.*, 1903, No. 29, p. 669.

Pick, L.—"Der Schilddrüsenkrebs der Salmoniden. Aus dem Laboratorium der L. und T. Landau'schen Frauenklinik, Berlin," *Berl. klin. Woch.*, 1905, pp. 1435-1542.

Pick, L., und Poll, H.—"Ueber einige bemerkenswerte Tumorbildungen aus der Tierpathologie, insbesondere über gutartige und krebsige Neubildungen bei Kaltblütern," *Berl. klin. Woch.*, 1903, Vol. XL, pp. 518, 572, Abstr. in *Jour. Am. Med. Assn.*, Aug. 8, 1903, p. 401; also "Weitere Untersuchungen über das Carcinom bei Kaltblütern," *Deutsch. med. Woch.*, Leipz. u. Berl., 1905, xxxi, 1817.

Pick, L.—"Der Schilddrüsenkrebs der Salmoniden (Edelfische) ein Beitrag zur vergleichenden Pathologie des Carcinoms," *Berl. klin. Woch.*, 1905, xlii, 1435-1440.

Plehn, Marianne.—"Ueber Geschwülste bei Kaltblütern, *Wien. klin. Woch.*, 1912, xxv, p. 691; also, *Ztschr. f. Krebsf.*, 1906, 4, 525; "Bösartiger Kropf (Adenocarcinom der Thyreoidea) bei Salmoniden," *Allg. Fischerei-Ztg.*, München, April 1, 1902, No. 7, pp. 117-118; "Ueber eigentümliche Drüsenzellen im Gefässsystem und in anderen Organen bei Fische," Anat. Anzeiger, 1906.

Plehn, Marianne.—"Ueber Geschwülste bei neideren Wirbeltieren," Travaux de la deuxième conférence internat. pour l'étude du cancer, Paris, 1910, p. 221. Discussion, p. 787.

Rous, Peyton F., Murphy, James B., and Tyler, N. H.—"Transplantable Tumors of the Fowl: a neglected material for cancer research," *Jour. Am. Med. Assn.*, June 1, 1912, Vol. LVIII, p. 1682; "The rôle of injury in the production of a chicken sarcoma by a filterable agent," *ibid.*, p. 1751; "The relation between a chicken sarcoma behavior and the growth's filterable cause," *ibid.*, p. 1840.

Ryder, John A.—"On a Tumor in the Oyster," Proc. Acad. of Nat. Sci., April, 1887.

Smallwood, W. M.—"Adrenal tumours in the kidney of the Frog," *Anat. Anzeiger*, 1905, Vol. XXVI, p. 652-668.

Smith, H. M.—"Case of epidemic carcinoma of thyroid in fishes," *Washington Medical Annals,* 1909, Vol. VIII, p. 313.

Schlimpert, H.—"Tumor bei einem Kanarienvogel," *Ztschr. f. Krebsf.*, 1910, Vol. VIII, 526-528.

Schminke, A.—"Ein Teratome aus der Bauchhohle eines Hahns," *Zentralbl. f. allg. Path. u. pathol. Anat.*, 1909, Vol. XX, 9-11.
Simon, Hermann.—Ueber ein klinisch an Botryomykom errinerendes Fibrosarkom beim Esel: *Ztschr. f. Krebsf.*, 1913, 13, p. 73.
Sticker, Anton.—"Ueber den Krebs der Thiere, etc.," *Arch. für klin. Chirurgie*, 1902, Bd. LXV, pp. 616, 1023.
Spencer, W. G.—Trans. Path. Soc., London, Vol. XLI, 1890, p. 400 (Reporting a case of sarcoma involving all the mammary glands of a cat).
Tyzzer, E. E.—"Tumors in the Common Fowl," Fifth Report of the Harvard Cancer Commission, 1909, 133.
Williams, Joseph W.—"A Tumor in the Fresh-Water Mussel (Anadonta cygnea)," *Jour. of Anat. and Physiol.*, 1889-90, xxiv, p. 307.
Winckuroff.—"Einige seltene Geschwülste bei Tieren," Inaugural Dissert., Bonn, 1908.

Geographical and Ethnological

Adams, G. C.—"Cancer in Australia: a comparison with other countries, together with a specific treatment for the prevention and arrest of the disease," *The Lancet*, Lond., 1904, i, 422-498; also, "Cancer Research in Australia," *Emp. Rev.*, Lond., 1904, vii, 117-134.
de Azevedo Sodre, A. A.—"Frequencia do cancer no Brazil," *Brazil-med.*, Rio de Janeiro, 1904, xviii, 229-232. Transl. in *An. san. mil.*, Buenos Aires, 1904, vi, 785-799.
Bashford, E. F., and Murray, J. A.—"The Statistical Investigation of Cancer," Second Scientific Report, Imperial Cancer Research Fund, Part I, 1904.
Bashford, E. F.—"The Ethnological Distribution of Cancer," Third Scientific Report, Imperial Cancer Research Fund, 1908, p. 1.
Bashford, E. F.—"Heredity and Disease—Cancer Heredity," Proc. Roy. Soc. of Med., London, Nov. 18, 1908, Vol. II, Part I, R. S. M., 63.
Bashford, E. F.—Address on Cancer in Man and Animals, General Meeting of the Sixteenth International Medical Congress, Budapesth, September, 1909; *Lancet*, London, September 4, 1909, p. 694; *Berl. klin. Woch.*, Sept. 6, 1909, No. 36, p. 1637, and Sept. 16, 1909, No. 37, p. 1683.
Bericht über die von der Schwedischen Aertzengesellschaft veranstaltete Sammelforschung über die Krebskrankheit in Schweden während der zeit von Dec. 1, 1905, bis Feb. 28, 1906. Enstattet von dem Krebsforschungskomitee der Gesellschaft: *Ztschr. f. Krebsf.*, 1908-9, 7, pp. 3-44.
Bertelsen, A.—"Om Forekomsten af Cancer i Grönland (The Prevalence of Cancer in Greenland)," *Hosp.-Tid., Kobenh.*, 1904, 4, R., xii, 209-214.
Bland-Sutton.—"Evolution and Disease," London, 1890.
Bowers, W. C.—"The geographical distribution and the medical treatment of cancer," *Illinois Med. Jour.*, Springfield, 1904-5, n. s. vi, 448-452.
Brault, J.—"L'épithéliome chez les indigènes Mussulmans d'Algérie," Janus, Amst., 1905, x, 577-580.
Cancer in Spain, *Brit. Med. Jour.*, 1904, i, 99. (Official Statistics of Spain, 1900, and of Madrid, 1901.)
Casalis, E. W.—"The incidence of carcinoma in South Africa," *South African Med. Rec.*, Cape Town, 1910, viii, 302-307; also, *Transvaal Med. Jour.*, Johannesburg, 1910-11, vi, 119-124.

Delbet, P.—"Rapport annuel du Sécrétaire général," Bull. de l'assoc. franç pour l'étude du cancer, 1911, 4, 19.

Fibiger.—"Bericht des dänischen Cancer—Komites über die Zählungen der Krebskranken auf Island und auf den Farörn," *Ztschr. f. Krebsf.*, Berl., 1913, xiii, 68-72.

Fujinami.—"Ueber die Verbreitung des Carcinoms (Japanese text, German abstr.)," *Mitteil. d. med. Gesell. zu Tokyo*, 1905, xix, 559-588.

Haviland, Alfred.—"Climate, Weather and Disease." Being a sketch of the opinions of the most celebrated ancient and modern writers with regard to the influence of climate and weather in producing disease. London, 1856.

Haviland, Alfred.—"Geographical Distribution of Disease in Great Britain," First Edition, 1875; Second Edition, 1892.

Haviland, Alfred.—"The Medical Geography of Cancer in England and Wales," *The Practitioner*, 1899, lxii, n. s., ix, p. 400.

Haviland, Alfred.—"Abstracts of two papers: I. On the Geographical Distribution of Heart Disease and Dropsy in England and Wales; II. On the Geographical Distribution of Cancer in England and Wales. London, 1869; The Geographical Distribution of Heart Disease and Dropsy, Cancer in Females and Phthisis in Females in England and Wales. London, 1875; On the Influence of Clays and Limestones on Medical Geography, illustrated by the Geographical Distribution of Cancer amongst Females in England and Wales." Trans. of the VIIth Internat. Cong. of Hyg. and Demogr., August 10-17, London, 1891, Vol. X. Div. II. Demography, pp. 186-195.

Henson, W. W.—"Cancer in Kaffirs; suggested cause," *Guy's Hosp. Gaz.*, Lond., 1904, xviii, 131-133.

Hislop, P. W.—"Cancer in New Zealand," *Brit. Med. Jour.*, Lond., 1909, ii, 1222-1225.

Hoffman, Frederick L.—"The Menace of Cancer," Trans. Am. Gyn. Soc., 1913.

Hutchinson, Woods.—"Studies in Human and Comparative Pathology," London, 1901.

Juillerat.—"Les maisons à cancer à Paris," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, 3, 61.

Lazarus-Barlow, W. S.—"Malignant disease in India and in England (remarks suggested by paper of Dr. W. D. Sutherland)," Arch. Middlesex Hosp., Lond., 1904, iii, 92-99.

Lazarus-Barlow, W. S.—"A Note on Cancer in Iceland," Arch. Middlesex Hosp., 1905, Vol. V, p. 273.

Levin, Isaac.—"Cancer among the American Indians and its bearing upon the ethnological distribution of the disease." (From the Dept. of Pathol. of Columbia Univ., at the Coll. Phys. & Surg.) (George Crocker Res. Fund.) *Ztschr. f. Krebsf.*, 1910, 9, p. 422.

Lindemann, E.—"Ueber Krebsstatistik auf Helgoland," *Ztschr.*, Jena, 1904, L., 225-232.

McConnell, G.—"A Review of Cancer in the United States According to the 12th Census," *Jour. Am. Med. Assn.*, 1906, 8, lvi, p. 1273.

McConnell, Guthrie.—"Die Krebskrankheit in der Vereinigten Staaten von Nord-Amerika—With map of U. S.," *Ztschr. f. Krebsf.*, 1908, Vol. VII, p. 238.

Maxwell, J. P.—"The Incidence of Malignant Disease in Hot Countries," *Jour. Trop. Med.*, Lond., 1904, vii, 270.

Murray, J. A.—"The Zoölogical Distribution of Cancer," Third Scientific Report, Imperial Cancer Research Fund, 1908, pp. 45-47.

Neve, E. F.—"Decade of Tumor Surgery in Kashmir Mission Hospital," *Indian Med. Gazette,* May, 1902, p. 164.

Peiper, Otto.—"Ueber Geschwülste in Deutschlands Kolonien. Eine Kasuistik u. Statistik der gut und bösartigen Geschwülste mit besonders Berücksichtigung deutsch ost-Afrikas," *Ztschr. f. Krebsf.,* 1912-13, 12, 291-366.

Power, D'Arcy.—"The Local Distribution of Cancer and Cancer Houses," *The Practitioner,* Lond., 1899, Vol. IX, n. s., p. 418.

Renner.—"Prevalence of malignant disease among natives of Sierra Leone," Select. Colon. Mag. Rep., 1901-2, Lond., 1904, pp. 224-226.

Robertson, Alexander.—"Cancer in the Gilbert Islands," *Jour. of Tropical Medicine,* Nov. 1, 1905, p. 317.

Sandwith, F. M.—"The Geographical Distribution of Cancer," *Clin. Jour.,* London, 1909-10, xxxv, p. 409.

Seligmann, C. G.—"On the Occurrence of New Growths among the Natives of Brit. New Guinea," Third Scientific Report Imperial Cancer Research Fund, 1908, p. 26.

Soegaard, Munch.—"Die Krebsformen Norwegens," *Ztschr. f. Krebsf.,* 1913, 13, p. 89.

Special Report on Cancer in Ireland, with statistical tables, and observations as to the prevalence of the disease; also notes on the history of cancerous cases, Dublin, 1903, Cahill & Co.; also, *Brit. Med. Jour.,* Lond., 1903, i, 1442.

Sutherland, David W.—"The Statistics of Malignant Disease Admitted to the Mayo Hospital, Lahore, Punjab, India, from 1892 to 1903 Inclusive," Archives of the Middlesex Hosp., Third Report from the Cancer Research Laboratories, 1909, p. 84.

Tomes, A.—"A run of cancer cases," *Indian Med. Gaz.,* Calcutta, 1880, xv, 183-185.

Williams, W. Roger.—"The Natural History of Cancer," 1908.

STATISTICS

Annual Report of the Public Health Committee of the London County Council, 1908.

Annual Report of the Registrar-General for 1911, Vol. LXXIV, p. 77 (England and Wales).

Baker, W. M.—"Contribution to the statistics of cancer," Med. Chir. Trans., London, 1862, xlv, 389-406; also, Proc. Roy. Med. & Chir. Soc., Lond., 1862, iv, 129-131.

Ball, Walter.—"Menstruation, Childbirth, and Cancer: a Statistical Study based on the Records of the Middlesex Hospital," Arch. Middlesex Hosp., 1906, vii, pp. 107-117.

Bashford, E. F.—"A Review of Recent Cancer Research," The Middleton-Goldsmith Lectures, New York Pathological Soc., October 2 and 4, 1912.

Bashford, E. F.—"Discussion on the Influence of Heredity on Disease," Proc. Roy. Soc. of Med., London, November, 1908, Vol. II, R. S. M. 63.

Bashford and Murray.—"The Statistical Study of Cancer," Second Scientific Report, Imperial Cancer Research Fund, 1905, Part I.

Behla, R.—"Ueber die Sterblichkeit an Krebs in Preussen während der Jahre 1903-1911 nach Alterklassen," *Berl. klin. Woch.,* 1913, L, 892.

Bulkley, L. D., and Janeway, H. H.—"A Study of 400 cases of epithelioma, in private practice, with remarks on treatment and results," *Medical Record*, New York, Mar. 2, 1908, p. 465.

Butlin, Sir Henry T.—"Proposed letter to the Registrar-General of England of Births, Deaths, and Marriages on the subject of the increase of Cancer drawn up by Mr. Butlin, of which the following is a copy," Proc. of Council, *Brit. Med. Jour.*, Nov. 12, 1887, p. 1070.

Butlin, Sir Henry T.—"Evidence given in 'Report of the Departmental Committee on Compensation for Industrial Diseases,'" London, 1907, p. 9.

Butlin, Sir Henry T.—"Discussion on the Influence of Heredity on Disease, with special reference to Tuberculosis, Cancer, and Diseases of the Nervous System," Proc. Roy. Soc. of Med., London, November, 1908, Vol. II, R. S. M. 75.

Census of England and Wales, 1911, Vol. VII, Ages and Condition as to Marriage, London, 1913.

Cripps, Harrison.—"Cancer of the Rectum," London, 1880.

Coley, W. B.—"The increase of cancer," *South. Med. Jour.*, Nashville, 1910, iii, 287-292; also Trans. South. Surg. & Gynec. Assn., 1909 (Phila.), 1910, xxii, 536-550; *Surg. Gynec. and Obst.*, Chicago, 1910, x, 591-597.

Ebel.—"Zur Statistik des Carcinoms der Unterlippe," *Beitr. z. klin. Chir.*, Vol. xii, Hft. 3.

Foulerton, A. G. R., and Hillier, W. T.—"Statistics of 667 Cases of Malignant Disease, 1900-1902," Arch. Middlesex Hosp. (Cancer Res.), 1904, ii, p. 148.

Girard. A. C.—"Report on cases of malignant disease observed at the United States Army General Hospital, at the Presidio, San Francisco, Calif., 1899-1902," *Jour. Am. Mil. Surg. U. S.*, Carlisle, Pa., 1904, xiv, 19-27.

Green, C.—"The Cancer Problem, a statistical Study," Edinburgh, 1912, 2d ed.; 3d. ed., Edin. and Lond., 1914.

Introduction, Fourth Scientific Report, Imperial Cancer Research Fund, 1911.

Johnson, Raymond, and Lawrence, F. W. P.—Article on Tumors, in A System of Surgery, edited by C. C. Choyce, Vol. I.

Jones, C. H.—"A Review of 3,676 deaths due to cancer in Baltimore City from 1891-1904 inclusive," *Jour. Alumni Assoc. Coll. Phys. & Surg.*, Balt., 1905-6, viii, 75-84.

Juliusberger, P.—"Siebentausend ein und achtzig Todesfälle an Krebs von 1885-99 bei der Friedrich Wilhelm preussischen Leben und Garantie Versicherungs-Gesellschaft in Berlin," *Ztschr. f. Krebsf.*, Berl., 1905, iii, 106-131.

King, George, and Newsholme, Arthur.—"On the Alleged Increase of Cancer," Proc. Royal Society of London, Vol. LIV, 1893, p. 209.

Körber, E.—"Die Ergebnisse der Hamburgischen Krebsforschung im Jahre 1908," Jahrb. d. Hamb. Staatskr.-Anst., Suppl. zu Bd. XIII, 1909.

Krasting, Karl.—"Beitrag zur Statistik und Kasuistik metastatischer Tumoren, besonders der Carcinommetastasen im Zentral nervensystem (auf. Grund von 12,730 Sektionen der path-anatom. Anstalt, Basel)," *Ztschr. f. Krebsf.*, 1906, iv, p. 315.

Lazarus-Barlow, W. S.—"Statistics of Carcinoma based on the records of the Middlesex and the St. George's Hospitals," Arch. Middlesex Hosp., Lond., 1904, iii, 128-164, 4 ch.

Lazarus-Barlow, W. S.—"Statistics of the site incidence of Carcinoma, based on the Records of the Middlesex Hospital (Cancer Res.) 1905," iv, 47.

Lazarus-Barlow, W. S.—"Malignant Disease of the Breast: A Statistical Study of the Records of Middlesex Hospital (Cancer Res.)," 1905, iv, 83.

Lazarus-Barlow, W. S.—"Cancer Ages": A Statistical study based on the cancer records of the Middlesex Hospital, Arch. Middlesex Hosp., 1905, Vol. V, p. 26 (Fourth Rep. from the Cancer Research Laboratories).

Le Conte, J.—"Statistical research on Cancer," *South. Med. and Surg. Jour.*, Augusta, 1846, n. s. ii, 257-293; also, "Vital Statistics illustrated by the laws of mortality from cancer," *West. Lancet,* San Francisco, 1872, i, 176-180.

Levin, Isaac.—"The Study of the Etiology of Cancer based on Clinical Statistics," Crocker Special Research Fund, 1912, Vol. II, p. 29.

Leyden, H.—"Bericht über die am 1 September, 1902, in Spanien veranstaltete Krebssammelforschung," *Ztschr. f. Krebsf.,* Jena, 1903, i, 41-72.

McConnell, Guthrie.—"Die Krebskrankheit in den Vereinigten Staaten von Nordamerika," *Zeit. f. Krebsf.,* 1908, Bd. VII, p. 238.

McGlinn, John A.—"Cancer Mortalities, 1890-1900," *Jour. Am. Med. Assn.,* May 15, 1909, p. 1610.

Maniulow, A.—"Die Mortalität in Folge von Krebsleiden in den Petersburger städtischen Hospitälern für die Jahre 1890-1900," Leipz., 1904, xlvi, 73-80.

Murray, J. H.—"Cancerous Ancestry and the Incidence of Cancer in Mice," Fourth Scientific Report, Imperial Cancer Research Fund, 1911, p. 114.

Newsholme, Arthur.—"The Statistics of Cancer," *The Practitioner,* April, 1899, Vol. LXII, n. s., ix, p. 371.

Neves, Azevedo.—"A mortalidad pelo cancro e outros tumores malignos en Portugal (annos de 1902, 1903, e 1904)," *Med. Contemp.,* Lisb., 1906, xxiv, 280-286.

Neves, Azevedo.—"Bericht über die Zählung der im Mai und Juni, 1904, in Portugal in ärtzlicher Behandlung gewesene Krebskranken," *Ztschr. f. Krebsf.,* 1908-9, pp. 297-330.

Oertel, H.—"The Inaccuracy of American Mortality Statistics," *American Underwriter,* May, 1913, Vol. XXXIX, No. 5.

Paget, Sir James.—"Lectures on Clinical Pathology," Vol. II, London, 1853.

Park, Roswell.—"A Further Inquiry into the Frequency and Nature of Cancer," *The Practitioner,* 1899, Vol. LXII, n. s., ix, p. 385.

Park, Roswell.—"The Nature of the Cancerous Process," IIme Congrès de la Société Internationale de Chirurgie, Brussels, Sept. 21-25, 1908, Vol. II, pp. 321 and 338.

Plowright, C. B.—"On the Distribution of Cancer Deaths in the Freebridge Lynn Rural District during the last forty-one years," *Med. Mag.,* Lond., 1903, xii, 813-822.

Rahts.—"Ergebnisse der Todtenursachenstatistik. Die Sterbefälle im deutschen Reiche während des Jahres 1906." A special reprint from Medizinal-statistische Mitteilung aus dem K. Gesundheitsamte. 1907, X, pp. 213-243.

Rieck, Joh., und Heinrich, Friedrich Martin.—"Krebsstatistik nach den Befunden des Pathologischen Instituts zu München vom Jahre 1854-1903," München, 1904.

Rosenfeld, Siegfried.—"Kritik bisheriger krebstatistiken mit vorschlägen für eine zukünftige Oesterreichiesche Krebsstatistik," Wien and Leipz., 1911.

Rowntree, C. W.—"Malignant Disease of the Tongue: A Statistical Study based on the Records of the Middlesex Hospital," Arch. Middlesex Hosp., 1906, vii, p. 131; also "Malignant Disease of the Lip," *ibid.*, p. 118.

Special Report on Cancer in Ireland, with Statistical Tables, and Observations as to the Prevalence of the Disease; also Notes on the history of cancerous cases. Dublin, 1903, Cahill & Co.; see also *Brit. Med. Jour.*, Lond., 1903, i, 1442.

Sutherland, D. W.—"Statistics of Malignant Disease admitted to Mayo Hospital, Lahore, Punjaub, India, 1892-1903," Arch. Middlesex Hosp., 1904, iii, 84.

Tanchon.—"Recherches sur la fréquence du cancer," *Gaz. d. Hôp.*, Paris, 1843, 2s., v, 313; also transl. *J. de Chir. in Augenh.*, Berl., 1843, n. f., ii. 514; *Ann. univ. di med.*, Milano, 1844, cx, 225; "Sur la fréquence croissante des cancers," Compt. rend. Acad. d. Sci., Paris, 1844, xviii, 878.

Theilhaber, F.—"Zur Lehre von dem Zusammenhang der sozialen Stellung und der Rasse mit der Anstechung der Uteruscarcinome," *Zeitsch. f. Krebsf.*, Bd. viii, 1909, p. 466.

Theilhaber, Felix A.—"Die Berliner Krebssterblichkeit; ein Beitrag zur Krebsstatistik," *Ztschr. f. Krebsf.*, 1912-13, 12, p. 367.

Theilhaber, A.—"Der Einfluss des Lebensalters auf die Entstehung des Carcinoms," *Med. Klin.*, Berl., 1913, ix, 1805.

Thirteenth Annual Report of the State Department of Health (New York), 1909, Vol. I, pp. 177-178.

Weinberg und Gastpar.—"Die bösartigen Neubildungen in Stuttgart von 1873-1902," *Ztschr. f. Krebsf.*, Jena, 1904, ii, 195-260.

Werner, R.—"Statistische Untersuchungen über das Vorkommen des Krebes in Baden, und ihre Ergebnisse für die ätiologische Forschung," Tübingen, 1910.

Site-incidence

Anschutz, Willy.—"Beiträge zur Klinik des Dickdarmkrebes," *Mitteil. a. d. Grenzg. der Med. u. Chir.*, 1907, No. XIV, p. 488.

Bainbridge, W. S.—"A Case of extensive Carcinoma of Tongue and Neck, presenting points of special interest," *American Medicine*, Mar. 25, 1905.

Baumgartner, Amédée.—"Maladies de la mamelle," Paris, 1913; also, "Nouveau Traité de Chirurgie," 1913, v. 23.

Beadles, Cecil F.—"Gall-stones and Cancer: (A letter in reply to statements by Roger Williams)," *Brit. Med. Jour.*, 1893, ii, p. 555.

Beatson, (Sir) George Thomas.—"Case of rapidly growing fibro-adenoma of Mamma," *Edinb. Med. Jour.*, 1908, Vol. I, p. 416.

Billroth, C. A. T.—"Die Krankheiten der weiblichen Brustdrüsen," 1880, Vol. VI.

Bland-Sutton, J.—"The Clinical Aspects of Metastatic Cancer of the Ovary." A paper read before the Med. Soc. of Lond., Oct. 24: *The Lancet*, Lond., 1910. 1277.

Butlin, Sir Henry.—"Illustrations of Very Early Conditions of Cancer of the Tongue," *Brit. Med. Jour.*, May 26, 1906. (With colored plate of clinical appearances and histological illustrations.)

Butlin, Henry T.—"An Address on the Results of Operation for Cancer of the Tongue," *Brit. Med. Jour.*, 1909, i, p. 1.

Cornil, Gervais.—"Étude sur le cancer du cœur," Paris, 1902; *Thèse de Paris*, 1901-2.

Cornil, V.—"Lymphangite cancéreuse de poumon," Compt. rend. soc. de biol., Par., 1879, 6s, iv., 130-133.

Cornil, V., et Campenon, V.—"Deux tumeurs du sein chez l'homme," Bull. et Mém. Soc. anat. de Paris, 1906, lxxxi, 94-97.

Cornil, V.—"Inoculabilité du cancer," "Les Tumeurs du Sein," Paris, 1908, Chap. XI, p. 329; "Cancer double des seins," p. 399.

Cornil, V.—"Les Tumeurs du Sein," Paris, 1908, pp. 163-186.

Delbet et Herrenschmidt.—"Épithéliome kystique mucoide du sein," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, 3, 106.

Delbet, Pierre, et Herrenschmidt, A.—"Tumeur mixte de la parotide," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, 3, p. 41.

Depage.—"Sarcome volumineux de la prostate; prostatectomie; guérison," *Jour. de Chir.*, Brux., 1908, viii, 372.

Depage.—"Cancer aberrant du rein," *Jour. de Chir.*, Brux., 1909, ix, 77.

Gosset, A., et Masson, P.—"Cancer intestinal de l'estomac," *Presse méd.*, Mar. 16, 1912, xx, 225-228.

Greene, W. H. Clayton.—"Some Tumours of the Breast," *The Practitioner*, 1905, n. s., xxii, p. 743.

Hammerschlag, Albert.—"Untersuchungen über das Magencarcinom," *Arch. f. Verdauungskr.*, 1896, Vol. II, pp. 1, 198.

Hani.—"Ueber das primäre Carcinom der Gallenwege," Zurich, 1903.

Hansen, P. N.—"Beitrag zur Lehre von den Sarkomen des Uterus," *Nord med. Arkiv.*, 1903, Abt. 1, No. 15.

Hippel, B.—"Zur Kenntnis der Mischgeschwülste der Leber," *Virchow's Archiv*, 1910, 201, p. 326.

Keen, W. W.—"Enormous mixed tumor of the parotid region," etc., Tr. Coll. Phys., Phila., 1904, xxvi, 83-91.

Keller, Konrad.—"Ein Fall von primärem Krebs des Gallenblasenhalses," München (In *Ztschr. f. Krebsf.*, 1906, 4, 104, ref. under Berichte). (University publication.)

Kemp. R. C.—"Diseases of the Stomach, Intestines, and Pancreas," 2d ed. W. B. Saunders, Phila. and Lond., 1912.

Kudo, T.—Das primäre Carcinom der Appendix. *Ztschr. f. Krebsf.*, 1907-08, Vol. VI, p. 402.

Lazarus-Barlow, W. S., and Taylor, W. Gordon.—"Statistics of the site incidence of carcinoma based on the records of the Middlesex Hospital," Arch. of the Middlesex Hosp., 1905, Vol. V, p. 46 (Fourth Rep. from the Cancer Research Laboratories).

Ledoux-Lebard.—"Sur une énorme tumeur de la region sacrococcygienne," Bull. de l'assoc. franç. pour l'étude du cancer, 1912, 5, 117.

Letulle et Weinberg.—"Appendicite et cancer primitif de l'appendice ileocœal," Bull. et mém de la soc. anat. de Paris, April, 1900, p. 374.

Martin, Hermann.—"Ein Fall von primären Cancroid der Lunge," *Ztschr. f. Krebsf.*, 1913, 13, p. 446.

Mayo, Wm. J.—"Cancer of the Stomach, with report of one hundred gastric resections," *Jour. Am. Med. Assn.*, April 7, 1906. On p. 1003 under Diagnosis.

Mayo, Wm. J.—"Carcinomata of the Gastro-Intestinal Tract," *Buffalo Medical Journal,* January, 1912, Vol. LXVII (1911-12), p. 305.

McDonald, Ellice.—"Fibromyoma of the Uterus Complicated by Cancer or Sarcoma, with Report of 35 Cases," *Jour. Am. Med. Assn.,* Mar. 20, 1909, Vol. LII, p. 952.

Monsarrat, K. W.—"A Malignant Growth of the Kidney," *Brit. Med. Jour.,* 1910, i, p. 686.

Monsarrat, K. W.—"Carcinoma of the Rectum," *The Lancet,* Lond., 1913, i, p. 390.

Morris, (Sir) Henry.—"Malignant Disease of the Stomach Associated with Malignant Disease of the Glands Above and Behind the Inner Extremity of Each Clavicle," *The Lancet,* Lond., Aug. 15, 1908, Vol. II, p. 446.

Moschcowitz, A. V., und Moschcowitz, E.—"Zur Appendizitisfrage: Ein Bericht über 2,000 konsekutive Falle von Erkrankungen der Appendix vermiformis mit besonderer Berücksichtigung der Therapie," *Arch. f. klin. Chir.,* 1907, Vol. 82, Hft. 3.

Oberndorfer.—"Appendixtumoren," *Ergebn. d. allg. Pathol. u. pathol. Anat.,* 1909, 13, pp. 586-592. Discussion, Verhandl. d. Deutsch. Pathol. Gesell., Erlangen, 1910.

Payr, E.—"Lebergeschwülste": II Cong. Int. Soc. de Chir., Brux., Sept. 21-25, 1908, Vol. II, p. 343. On page 536 he refers to tumors of the gall-bladder, carcinoma, etc., and in Part III to neoplasms of gall-bladder, etc., pp. 556-603. (Reports.)

Petersen W., und Colmers, F.—"Anatomische und klinische Untersuchungen über die Magen und Darmkarcinome," *Beitr. z. klin. Chir.,* 1904, Vol. XLIII, 1-196.

Podwyssozki, W. (St. Petersburg).—"Neue Ansichten zum Begrundung der Reiztheorie des Krebses und der bösartigen Geschwülste," *Ztschr. f. Krebsf.,* 1908-9, vii, p. 286. (An address at the initiatory session of the Internat. Assoc. for Cancer Res., May 23, 1908, in Berlin.)

Pollitzer, S.—"Cancer en cuirasse," *Jour. Cut. Dis.,* Apr., 1909, xxvii, p. 143.

Rogg, Franz Alfons.—"Carcinom und Carcinoid der Appendix," *Ztschr. f. Krebsf.,* 1913, xiii, p. 12.

Rokitansky.—"Beiträge zu der Erkrankungen des Wurmfortsatzes," *Wien. med. Presse,* 1866, vii, No. 26, p. 675; also, "Ueber gallertkrebsiger Erkrankung des Wurmfortsatzes," *Med. Jahrbücher,* 1867, Vol. III.

Rolleston, H. D., and Jones, Lawrence.—"Primary Malignant Disease of the Vermiform Appendix," Med.-Chir. Trans., 1906, Vol. 89, pp. 125-156; Roy. Med. and Chir. Soc., Feb. 27, 1906; *Am. Jour. Med. Sci.,* 1906, cxxxi, 951; *The Lancet,* June 2, 1906, Vol. I, p. 1525.

Rouville et Martin.—"Tumeur mixte de la parotide d'un volume remarquable," Bull. et mém. soc. anat. de Paris, 1904, lxxix, 659.

Ryall, Charles.—"A Lecture on Cancer of the Tongue" (delivered at the Cancer Hospital, Brompton, on February 12, 1913), *Brit. Med. Jour.,* Apr. 3, 1913, i, p. 697.

Simon, Hermann.—"Sarkomentwicklung auf einer Narbe," *Ztschr. f. Krebsf.,* 1910-11, x, 210.

Stieda.—"Appendicitis und Carcinoma des Processus," *Reichs-med. Anzeiger,* 1910, xxxv, No. 3, p. 163.

Voeckler, Th.—"Ueber den primären Krebs des Wurmfortsatzes," *Arch. f. klin. Chir.*, 1908, 86, 477.

Winkler.—"Krebs des Wurmfortsatzes," Verhandl. der deutsch path. Gesell., Erlangen, 1910.

ETIOLOGY, HISTOPATHOLOGY, CANCER RESEARCH

Abderhalden, E., und Medigreceanu, F.—"Zur Kenntnis der peptolytischen Fermente verschiedener Krebse und anderer Tumorarten," *Hoppe-Seyler's Ztschr. f. physiol. Chem.*, 1910 (in collaboration with the Bacteriol. Dept., London Hosp.); also, III Communication: *ibid.*, 1910, Vol. LXVI.

Abramowski.—"Disposition und Irritation bei Krebs," *Ztsch. f. Krebsf.*, 1910-11, x, p. 235.

Abramowski.—"Zur parasitären Krebstheorie," *Ztschr. f. Krebsf.*, 1910, Vol. ix, 385.

Abramowski.—"Ueber die Biologie des Krebses," *Ztschr. f. Krebsf.*, Berl., 1913, xiii, 345-352.

Acton, H. W.—"Melanotic Sarcomata," *Middlesex Hosp. Jour.*, Lond., 1905, ix, 51-67.

Adami, I. George.—"The Principles of Pathology," London, 1909.

Adamkiewicz.—"Ueber die Anstechung und die Erblichkiet des Krebserregers, Aertzl. Rundschau, München, 14th year, No. 41.

Albrecht, Eugen.—"Die Grundprobleme der Geschwulstlehre," Frankfurter Ztschr. f. Pathol., 1907, Vol. I, p. 221-247.

Albrecht, Eugen.—"Randbemerkungen zur Geschwulstebre," Frankfurter Ztschr. f. Pathol., 1907, Vol. I, p. 607.

Alibert.—"De la contagion du Cancer," cit. from Michaux, *Sem. méd.*, 1889, ix, 238.

Apolant, Hugo.—"Die epithelialen Geschwülste der Mäuse," Arbeit aus dem konigl. Inst. f. exper. Therap. zu Frankfurt a. M., 1906-8, (Parts 1-4), Pt. I, p. 1.

Apolant, H.—"Ueber Krebsimmunität," *Zeitschr. f. Krebsf.*, 1911, xi, 97.

Apolant, H.—"The Question of Immunity," *Jour. of Exper. Med.*, 1911, xiv, 316.

Apolant, Hugo.—"Die experimentelle Erforschung der Geschwülste (Das Material der experimentelle Geschwülstforschung und die Technik der Impfung)," Handbuch der Pathogenen Micro-organismen; Herausgegeben von Kolle u. Wassermann, 1913; Bd. III, p. 176.

Aschoff, L.—"Ueber Spontaninfektion," *Zentralbl. f. Gynäk.*, Leipz., 1911, xxxv, 1050-1052.

Bainbridge, W. S.—"A Brief Résumé of the World's Recent Cancer Research," *Medical Record*, New York, Sept. 1, 1906.

Bainbridge, W. S.—"Transmissibility and Curability of Cancer," *Boston Med. and Surg. Jour.*, Vol. CLVI, No. 26, p. 835, June 27, 1907.

Barret, J. O. Wakelin.—"The Experimental Production of Retrogression of Implanted Mouse Carcinoma," *Ztschr. f. Krebsf.*, 1913, xiii, p. 415.

Barwell, Richard.—"On Acute Traumatic Malignancy," *Brit. Med. Jour.*, Feb. 11, 1882, i, p. 187.

Bashford, E. F.—"Cancer Problems," *Brit. Med. Jour.*, July 18, 1903, No. 2220, p. 127.

Bashford, E. F.—"The Growth of Cancer Under Natural and Experimental Conditions," Sci. Reports on the investigations of the Imp. Cancer Res. Fund, Part 2, Lond., 1905; also "The Statistical Investigation of Cancer," *ibid.*, No. 2, 1905.

Bashford, E. F.—"Quelles épreuves scientifiques a-t-on aujourd'hui de la nature parasitaire des néoplasies, spécialement du cancer?" XV Cong. Int. de Méd., Lisbon, 1906.

Bashford, E. F.—"Illustrations of Propagated Cancer," *Brit. Med. Jour.*, 1906, I, p. 1211.

Bashford, E. F.—"Classification des Sarcomes," XV^{me} Cong. Int. de Méd., Lisbon, 1906.

Bashford, E. F.—"L'État actuel de la Question du Cancer," *Rev. scientif.*, June 2, 1906.

Bashford, E. F.—"Are the Problems of Cancer Insoluble?" *Brit. Med. Jour.*, 1905, ii, 1507.

Bashford, E. F.—"The Problems of Cancer," *Brit. Med. Jour.*, July 18, 1908.

Bashford, E. F.—"Heredity in Cancer," Proc. Roy. Soc. Med., Jan., 1909.

Bashford, E. F.—"Ueber den Krebs der Menschen und der Tiere," *Berl. klin. Woch.*, 1909, No. 37.

Bashford, E. F.—"A Review of Recent Cancer Research," The Middleton-Goldsmith Lectures, New York Pathological Society, October 2 and 4, 1912.

Bashford, E. F.—"The Constancy and Variability of Tumour Cells During Propagation," 17th Internat. Congr. of Med., Lond., 1913, iii, Aug. 6 (Independent Paper), p. 59.

Bashford and Murray.—"The Significance of the Geographical Distribution of Cancer," First Annual Report, Imperial Cancer Research Fund, 1903.

Bashford, E. F., and Murray, J. A.—"On the Genesis of Mouse Tumours," Second Scientific Report, Imperial Cancer Research Fund, London, 1905, No. 2, Pt. II, 15.

Bashford and Murray.—"On the Occurrence of Heterotypical Mitoses in Cancer," Proc. Roy. Soc., B, Vol. LXXVII, 1906.

Bashford, E. F., and Murray, J. A.—"Carcinoma Mammæ in the Mouse," *The Lancet*, Lond., Mar. 23, 1907, p. 798.

Bashford, E. F., Murray, A. F., and Bowen, W. H.—"The Experimental Analysis of the Growth of Cancer," Proc. Roy. Soc., Lond., 1906, S.B. LXXVIII, 195-222.

Bashford, E. F., Murray, J. A., and Cramer, W.—"The Natural and Induced Resistance of Mice to the Growth of Cancer," Proc. Roy. Soc., Ser. B., Vol. LXXIX, p. 164-165. Read Jan. 17, 1907.

Bashford, E. F., Murray, J. A., and Cramer, W.—"Transplantation of Malignant New Growths," Sci. Rep. of Imp. Cancer Res. Fund, 1905, No. 2, p. 13.

Bashford, E. F., Murray, J. A., and Haaland, N.—"The Induction of Specific Resistance and of General Enhanced Susceptibility to Inoculation of Carcinoma in Rats and Mice," *Jour. Pathol. and Bacteriol.*, 1908, Vol. XII, pp. 435-439.

Bashford, Murray, Haaland.—"Ergebnisse der experimentelle Krebsforschung," *Berl. klin. Woch.*, 1907, Nos. 38 and 39.

Bashford, E. F., and Russell, B. G. R.—"Further Evidence on the Homogeneity of the Resistance to the Implantation of Malignant New Growths," *The Lancet*, Lond., Mar. 19, 1910.

Beard, J.—"Ueber Embryomata und andere Geschwülste," *Berl. klin.*

Woch., 1903, No. 30; also "Die Embryologie der Geschwülste." *Zentralbl. f. allg. pathol. Anat.*, 1903, Vol. XIV, No. 13. Cf. also "Carcinomliteratur" (*Beilage z. deutsch. Medizinal-Zeitung*), ii, No. 1.

Beatson, George T.—"Etiology of Carcinoma: Has It a Physiological Function in the Body?" *Brit. Med. Jour.*, 1905, i, 921.

Beck, Karl.—"Ueber Multiplizität primäre maligner Tumoren zugleich ein Beitrag zur Metaplasiefrage," *Virchow's Arch.*, 1909, 196, Hft. 2.

Beckton, H.—"On the Nature of the Changes Occurring in Altmann's Granules in Malignant Disease," Arch. Middlesex Hosp., Lond., 1913, xxx, 148-152.

Beebe, Silas Palmer.—"The Chemistry of Malignant Growths," II, "The Inorganic Constituents of Tumors," *Am. Jour. of Physiol.*, 1904, v, p. 12.

Benecke.—Ziegler's Beiträge zur path. Anat., 1892-1893.

Billroth, C. A. T.—"Ueber die Einwirkung lebenden Pflanzen und Thierzellen auf einander: eine biologische Studie," *Samml. med. Schrift.*, Herausg. v. d. *Wien. klin. Woch.*, No. 10.

Billroth.—"Krankheiten der Brustdrüse," *Deutsche Chirurgie,* Stuttgart, 1880.

Billroth, Th., und Czerny, Vincenz.—"Beiträge zur Geschwülstlehre. I. Ueber plexiform Geschwülste," *Arch. f. klin. Chir.*, 1869, Vol. II, p. 230.

Bondy, O.—"Zum Problem der Selbstinfektion," *Zentralbl. f. Gynäk.*, Leipz., 1911, xxxv, 1633-1639.

Borrel, A.—"Épithéliomes infectieuses et épithéliomas," Ann. de l'Inst. Pasteur, 1903, xvii, p. 81.

Borrel, A.—"Le Problème du Cancer," Bull. de l'Inst. Pasteur, 1907, Vol. V, p. 497.

Borrel, A.—"Le problème étiologique du Cancer," *Ztschr. f. Krebsf.*, 1908-9, 7, p. 265 (an address at the initiatory session of the Internat. Assoc. for Cancer Res. in Berlin, May 23, 1908).

Borrel, A.—"Parasitisme et tumeurs," Travaux de la deuxième conférence internat. pour l'étude du cancer, Paris, 1910, p. 193.

Borrel, A.—"Le Cancer," *Rev. scient.*, Paris, 1912, ii, 614-621.

Borrmann, Robt.—"Die Enstehung und das Wachstum des Hautcarcinoms," *Ztschr. f. Krebsf.*, 1904, Vol. II, pp. 1-170; also "Das Wachstum und die Verbreitungswege des Magencarcinoms," *Grenzg. der Med. u. Chir.*, 1901.

Borst, Max.—"Die Lehre von den Geschwülsten mit einem mikroskopischen Atlas," 2 vols., Wiesbaden, 1902.

Borst, Max.—"Ueber Wesen und Enstehung der Geschwülste," Würzburger Abhandlungen, 1906.

Bostrom, E.—"Traumaticismus und Parasitismus als Ursachen der Geschwülste," Giessen, 1902.

Bowen, John T.—"Precancerous Dermatoses: A Study of Two Cases of Chronic Atypical Epithelial Proliferation," *Jour. Cut. Dis.*, 1912, Vol. XXX, p. 241.

Bowen, W. H.—"The Effects of Surgical Interference with the Blood Supply on the Growth of Transplanted Carcinomata and Sarcomata," III Sci. Rep. Imp. Cancer Res. Fund, 1908.

Butlin, Sir Henry T.—"Cancer Is a Parasitic Disease," *Brit. Med. Jour.*, 1905, ii, 1565.

Butlin, Sir Henry T.—"Illustrations of Very Early Conditions of

Cancer of the Tongue," *Brit. Med. Jour.*, May 26, 1906 (with colored plate of clinical appearances and histological illustrations).

Butlin, Sir Henry T.—"On the Contagion of Cancer in Human Beings: Auto-inoculation" (Address in Surgery, delivered at 75th Ann. Meeting of the Brit. Med. Assn.), *Brit. Med. Jour.*, Aug. 3, 1907, p. 255.

Calkins, G. N.—"Biological Aspect of Carcinoma," *Ann. Surg.*, Phila., 1905, xlii, 794-797.

Calkins, G. N.—"Report on the Biological Work Done under the George Crocker Special Research Fund, 1909-11," "Studies in Cancer and Allied Subjects." Conducted under the George Crocker Special Research Fund at Columbia University, New York, 1913, III, pp. 1-5.

Calkins, G. N., and Clowes, G. H. A.—"Some Artefacts in Mouse Carcinoma," *Jour. Infect. Dis.*, Chicago, ii, 553-561.

Cameron, S. J. G.—"The Vascular System and Fibromyoma," *Glasgow Med. Jour.*, Sept., 1908.

Clowes, G. H. A.—"Action of Chemical Compounds on Cancer in Mice," in Rep. of New York State Cancer Laboratory, 29th Annual Rep. of Dept. of Health of the State of New York, 1908, Vol. I; also "Ueber die therapeutische Wirkung der Metalle auf Krebs," *Berl. klin. Woch.*, 1912, No. 43.

Clunet, J.—"Recherches expérimentales sur les tumeurs malignes," Steinheil, Paris, 1910.

Cohnheim.—"Vorlesungen über allgemeine Pathologie," Vols. 1 and 2, 2nd Ed., Berlin, 1882, pp. 723-736.

Coley, W. B.—"The Influence of Injury upon the Development of Sarcoma," *Annals of Surg.*, Phila., 1898, xxvii, p. 259.

Coley, W. B.—"Further Evidence in Support of the Theory That Hodgkin's Disease Is a Type of Sarcoma," Trans. Am. Surg. Assn., Phila., 1908, xxvi, 560-580.

Coley, W. R.—"Auto-Inoculation or Local Infectivity of Cancer," *Jour. Am. Med. Assn.* (Am. Assoc. for Cancer Res., Buffalo, Aug. 15, 1908), July 11, 1908, ii, p. 158. Abstr. and Discussion.

Coley, W. B.—"Injury as a Causative Factor in Cancer," *Annals of Surg.*, Phila., 1911, liii, 449; 615, 7 pls.

Coley, W. B.—"The Causal Relationship Between Injury and Cancer," *Surg. Gynec. and Obst.*, Chicago, 1911, xii, 189.

Copeman, S. Monckton, and Hake, J. Wilson.—"Report on a Study of the Variations of Hydrochloric Acid in the Gastric Contents of Mice and Rats as Compared with the Human Subject in Cancer," Third Scientific Report, Imperial Cancer Research Fund, 1908, p. 398.

Cornil, A. V., et Ranvier, L. A.—"Contribution à l'étude du dévelopement histologique des tumeurs épithéliales (cancroide);" Paris, 1866. Repr., *Jour. d'Anat. et de la Physiol.*

Cornil, V.—"Manual of Pathological Histology," Transl. Phila., 1880.

Cornil, V.—"Des Modifications des noyaux et des cellules cancéreuses qui peuvent en imposer pour des parasites," Atti d. XI Cong. med. internaz., Roma, 1894, ii, patol. gen. ed. anat. patol., p. 84-88.

Cornil, V.—"Sur le procédé de division indirecte des noyaux et des cellules épithéliales dans les tumeurs (épithéliome, carcinome, papillome)," *Arch. de Physiol. norm. et pathol.*, 1886, 3 s. 7-8, p. 310.

Cornil, A. V.—"Leçons sur l'anatomie pathologique des métrites, des salpingites, et des cancers de l'utérus faites à l'Hôtel Dieu." Paris, 1889.

Cornil, A. V.—"Contribution à l'histoire du développement histologique des tumeurs épithéliales (squirrhe, encéphaloide, etc.)," 80, Paris.

Cornil, V.—"Sur les greffes et inoculation du cancer," Bull. de l'Acad. de Méd., 1891, 3 s. xxv, 906-909.

Cornil, V.—"Mode de multiplication des noyaux et des cellules dans l'épithéliome," *Jour. de l'Anat. et Physiol.*, etc., Paris, 1891, xxvii, 97-116, 2 pls.

Cornil, V.—"Sur les types de l'inflammation dans les épithéliomes," Bull. Acad. de Méd., Paris, 1904, 3 s. li, 123-126.

Cornil, V., et Trasbot, L.—De la mélanose.—"Mémoire en réponse a la question posée par l'académie de médecine (prix postal) 'Des différentes espèces de mélanoses,' " Paris, 1868.

Councilman, W. T., and Magrath, G. B.—"The Lesions of the Skin and the Tumor Formations in Xeroderma Pigmentosum," Fifth Report of the Cancer Commission of Harvard Univ., 1909, p. 5.

Crile, George W.—"Hemolysis, with Special Reference to Cancer and Tuberculosis," *Jour. Am. Med. Assn.*, Dec. 12, 1908, li.

Czerny.—"Warum dürfen wir die parasitäre Theorie für die bösartigen Geschwülste nicht aufgeben?" *Bruns' Beitr. z. klin. Chir.*, Vol. xxv, p. 243.

Darier, J.—"Des affections précancéreuses de la peau et des muqueuses," Assoc. franç. pour l'étude du Cancer, Sess. July 20, 1908. (Suppl. in *Rev. de Méd.*, 1908, 28, pp. 59-69.)

Delbet, Pierre et Herrenschmidt.—"Envahissement des ganglions sous forme typique," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, iii, 324.

Dietrich, A.—"Die Karzinome des Wurmfortsatzes," *Deutsch. med. Woch.*, 1910, xxxvi, No. 13, pp. 610-613.

Ehrlich, P.—"Experimentelle Karzinomstudien an Maüsen," *Ztschr. f. ärtzl. Fortbildung,* 1906, iii, 205; also Arbeiten aus dem Kgl. Inst. für exper. Therap., 1906, Hft. 1, p. 75; Abhandlung der Internationalen Konferenz für Krebsforschung, Heidelberg, Sept. 25-27, 1906.

Ehrlich, P., and Apolant, H.—"Beobachtungen über maligne Maüsentumoren," *Berl. klin. Woch.*, July, 1905, 871.

Ehrlich and Apolant.—"Ueber die Genese des Carcinoms," Verhandl. deutschen path. Gesellsch., Kiel, 1908.

Engel, Salo.—"Ueber die Beziehungen zwischen Trauma und Gewachsbildung in Gehirn." Aus dem K. pathol-Inst. zu Breslau (Univ. Publication).

Eve, Sir Frederic.—"A Lecture on Melanoma," *The Practitioner,* London, February, 1903.

Ewing, James.—"Cancer," Harvey Lectures, New York, 1908.

Farmer, Moore, J. E., and Walker, C. E.—"A Cause of Malignancy in New Growths," *Brit. Med. Jour.*, Lond., 1903, ii, 1526-1528.

Farmer, Moore, and Walker.—"Resemblances Exhibited between the Cells of Malignant Growths in Man and Those of Normal Reproductive Tissue," Proc. Roy. Soc., Vol. 72, 1903.

Fibiger, J.—"Ueber eine durch Nematoden (Spiroptera sp. n.) hervorgerufene papillomatose u. karzinomatose Geschwultsbildung im Magen der Ratte," *Berl. klin. Woch.*, 1913, p. 289; also *Ztschr. f. Krebsf.*, 1913, xiii, 217.

Fibiger, J.—"Untersuchungen über eine Nematode," *Ztschr. f. Krebsf.*, 1913, pp. 217-280.

Fischer, B.—"Die experimentelle Erzeugung atypischer Epithelwucherungen und die Enstehung bösartiger Geschwülste," *Münch. med. Woch.*, 1906, No. 42.

Freund, E.—"Studien über die Disposition für Karzinom," *Münch. med. Woch.*, 1910, lvii, 722.

Freund, W. A.—"Zur Naturgeschichte des Krebskrankheit nach klinische Erfahrungen." *Ztschr. f. Krebsf.*, 1905, iii, pp. 1-33.

Freund E., und Kaminer, G.—"Ueber die Beziehungen zwischen Tumorzellen und Blutserum," *Wien. klin. Woch.*, 1910, No. 34; also *Biochem. Ztschr.*, Berl., 1910, xxvi, 312-324; also "Zur Diagnose des Carcinoms," *Wien. klin. Woch.*, 1911, No. 5.

Gay, Frederick P.—"A Transmissible Cancer of the Rat Considered from the Standpoint of Immunity," *Jour. Med. Res.*, Feb., 1909, xx, 175.

Gaylord.—"On the Evidence of Nuclear Division in Certain Cell Inclusions in Cancerous Epithelium," *Festschr. für Orth*, Berlin, 1903, No. 43.

Gaylord.—"Ueber die Bedeutung der Plimmerschen bezw. Sjöbringschen Körperchen und die durch menschlichen Material erzeugten Krebswucherungen bei Tieren," Verhandl. des Komitees f. Krebsf., 1903.

Gaylord.—"Mycetozoen im Carcinom, ihre Beziehungen zur Plasmodiophora brassicæ," etc., Ber. d. Naturf. Versamml. zu Karlsbad, 1903.

Gaylord, H. G.—"Parasitical Relations of Cancer," *Am. Pract. Surg.*, N. Y., 1906, i, 381-412.

Gierke, E.—"Die hemorrhagischen Mäusetumoren," Ziegler's Beiträge, 1908; also, "The Hemorrhagic Mammary Tumors of Mice, with Results of Research into Susceptibility and Resistance to Inoculation," III Sci. Rep. Imp. Cancer Res. Fund, 1908, p. 115.

Girard-Mangin.—"Les poisons cancéreux," Paris theses, 1908-9.

Girard-Mangin.—"Toxicité des liquides ascitiques et kystiques," Bull. de l'Assoc. franç. pour l'étude du Cancer," 1910, iii, 191.

Gockel, M.—"Ueber die traumatische Enstehung des Carcinoms mit besonderer Berücksichtigung des Intestinaltractus," *Arch. f. Verdauungskr.*, 1896, ii, p. 461.

Gray, F. P.—"A Transmissible Cancer of the Rat Considered from the Standpoint of Immunity," *Journ. of Medical Research*, xx, 176.

Gruber, Georg B.—"Beitrag zur Frage nach der Beziehung zwischen Krebs und peptischem Geschwür im oberen Digestionstrakt," *Ztschr. f. Krebsf.*, 1913, xiii, p. 105.

Guleke, N.—"Ueber Tumorbildung in versprengten Parotiskeimen," *Arch. f. klin. Chir.*, Vol. LXXXI, p. 275.

Haaland, M.—"Contribution to the Study of the Development of Sarcoma under Experimental Conditions," Third Scientific Report, Imperial Cancer Research Fund, 1908, p. 175.

Haaland, M.—"Spontaneous Tumors in Mice," Fourth Scientific Report, Imperial Cancer Research Fund, 1911, p. 1.

Haberfeld, Walther.—"Zur Statistik und Aetiologie des Carcinoms des Magens, Gallenwege und Bronchien," *Ztschr. f. Krebsf.*, 1908-9, vii, p. 190.

Haga, Ishio.—"Experimentelle Untersuchungen über die Erzeugung atypischer Epithel- und Schleimhautwucherungen" (for the Pathol. Inst. of the City Hosp., Urban, Berlin, Koch), *Ztschr. f. Krebsf.*, 1912-13, xii, p. 525.

Hahn, Ernst.—"Ueber Transplantation von Carcinomatöser Haut," *Berl. klin. Woch.*, 1888, xxv, 413-415.

Hanau.—"Erfolgreiche experimentelle Uebertragung von Carcinom," *Fortschr. d. Med.*, 1889, Vol. VII, p. 321.

V. Hansemann.—"Studien über die Spezificität, den Altruismus und die Anaplasia der Zellen," Berlin, 1893, in "Die mikroscopische Diagnose der bösartigen Geschwülste" (1st ed. Berlin, 1897; 2d ed., 1902); also, "Ueber Kernteilungsfiguren in bösartigen Geschwülsten," *Biol. Centralbl.*, Mar. 1, 1904, Vol. XXXIV, p. 189.

V. Hansemann, D.—"Ueber die Funktion der Geschwülstzellen," *Ztschr. f. Krebsf.*, 1906, iv, 565.

V. Hansemann, D.—"Formative Reize und Reizbarkeit," *Ztschr. f. Krebsf.*, 1908-9, Vol. VII, p. 69.

V. Hansemann.—"Beitrag zur Histogenese der Parotistumoren," *Ztschr. f. Krebsf.*, 1910, ix, p. 379.

V. Hansemann.—"Ueber die Benennung der Geschwülste," *Ztschr. f. Krebsf.*, 1913, xiii, p. 1.

Hansemann, D. von.—"Demonstration von Präparates des Herrn Fibiger zur künstlichen Erzeugung von Krebs," *Verhandl. ärtzl. Ges., Berl. med. Ges.*, Sitz, Mai 7, 1913, I, 988.

Hauser, Gustav.—"Das Cylinderepithel. Carcinom des Magens und des Dickdarms," Jena, 1890.

Hechinger.—"Ueber traumatische Entstehung des Sarkoms," *Inaug.-Diss.*, München, 1903.

Hegar, A.—"Theorie und Behandlung des Krebses," *Münch. med. Woch.*, 1904, No. 15, p. 644.

Hillier, W. S., and Tritsch, T.—"Heredity in Cancer," Arch. Middlesex Hosp. (Cancer Res.), 1904, ii, p. 143.

Hippel, B.—"Zur Kenntnis der Mischgeschwülste der Leber," *Virchow's Arch.*, 1910, Vol. CCI, Hft. 3.

Hutchinson, J.—"Cancer, Sarcoma, and Local Injury," *Brit. Med. Jour.*, Feb. 11, 1882, i, p. 197 (an editorial).

Israel.—"Die Probleme der Krebsätiologie," *Arch. f. klin. Chir.*, 1902.

Jaeger, Alfred.—"Die Enstehung des Melaninfarbstoffs," *Virchow's Arch.*, 1909, 198, p. 62.

Jaeger, Alfred.—"Der Ursachenkomplex der organotypen Tumorgenese: Die Enstehung des Krebses," *Ztschr. f. Krebsf.*, 1910, ix, p. 193-265.

Jensen, C. O.—"Uebertragbare Rattensarkome," *Ztschr. f. Krebsf.*, 1908-9, vii, p. 45.

Jensen, C. O.—"Ueber einige Probleme der experimentelle Krebsforschung," *Ztschr. f. Krebsf.*, 1908-9, vii, p. 278.

Justamond, J. O.—"An Account of the Methods Pursued in the Treatment of Cancerous and Scirrhous Disorders and Other Indurations," 1870.

Kappers, O. U. Ariens, und Van Roojen, P. H.—"Einige Bemerkungen über die microscopische Struktur der Magen und Darmcarcinom und ihre Verhältnisse zum macroscopische Bau," *Ztschr. f. Krebsf.* 1906, iv, 396.

Kaposi.—"Ueber combination von Lupus mit Karzinom," *Wien. med. Presse*, 1879, xx, 87-89; also, *Vierteljahrschr. f. Dermat.*, Wien, 1879, vi, 73-88, 1 pl.; also, *Anz. d. k. k. Gesell. d. Aerzte-Wien*, 1878.

De Keating-Hart.—"Researches on the Pathogenesis of Cancer," *Practitioner*, Lond., 1913, XCI, 445-459.

Klebs, E.—"Handbuch der pathologischen Anatomie," Berlin, 1869, i, p. 307.

Klemperer, G.—"Der jetzige Stand der Krebsforschung," Berlin, 1912.

Kolb, Karl.—"Der Einfluss des Berufes auf die Häufigkeit des Krebses" (Zweite Mittheilung des Bayerischen Komitees f. Krebsforschung), *Ztschr. f. Krebsf.*, 1910, ix, p. 445.

Kord-Lutgert, S.—"Darmsarkom nach Trauma," *Inaug.-Diss.*, München, 1907.

Krompecher, E.—"Der Basalzellenkrebs," Jena, 1903; G. Fischer.

Krompecher, E.—"Zur Histogenese und Histologie des Krebses," *Ztschr. f. Krebsf.*, 1912-13, xii, p. 373.

Landau, Moritz.—"Zur onkologischen Stellung der sogenannten 'verkalten Epitheliome' der Haut" (mit 2 Textfiguren), *Ztschr. f. Krebsf.*, 1912-13, Vol. XII, p. 506.

La Roy, L.—"Grands faits de l'expérimentation dans le cancer; leçon inaugurale," *Belgique méd.*, Gand, 1912, xix, 231-235.

Lazarus-Barlow.—"On the Presence of Radium in Some Carcinomatous Tumors," Proc. Roy. Soc., Lond., 1912-13, s. B., lxxxv, 170-173.

Lazarus-Barlow, W. S.—"On the Presence of Radium in Some Carcinomatous Tumors and Other Tissues," Archives of the Middlesex Hosp., Vol. XXVII, 1912.

Lazarus-Barlow, W. S.—"On the Presence of Radium in Some Gall-Stones and on a Correlation of This with the Frequency of Gall-Stone Occurrence in Carcinoma," Archives of the Middlesex Hospital, Vol. XXVII, 1912.

Legrand, L. (de Pekin).—"Multiplication cellulaire et cancer," Bull. de l'assoc. franç. pour l'étude du cancer," 1911, iv, 71.

Levesque, Georges.—"Contribution à l'étude des inoculations opératoires du cancer," Paris, 1903.

V. Leyden.—"Bericht über die vom Komitee f. Krebsf. am 15 Oct., 1900, veranstaltete Sammelforschung," Jena, 1902.

Levin, I.—"On the Pre-Cancerous State—an Experimental Study," Proc. New York Pathol. Soc., 1912, n. s., xii, p. 42.

Levin, Isaac.—"The Study of the Etiology of Cancer Based on Clinical Statistics," Crocker Spec. Res. Fund, 1912, Vol. II, p. 29.

Levin, Isaac.—"On the Mechanism of the Formation of Metastases in Malignant Tumors: An Experimental Study," Crocker Spec. Res. Fund, 1912, Vol. II, p. 115.

Levin, Isaac.—"Resistance to the Growth of Cancer Induced in Rats by Injection of Autolyzed Rat Tissue," Crocker Spec. Res. Fund, 1912, Vol. II, p. 11.

Levin, T.—"The Mechanism of Immunity in Experimental Cancer," *Med. Rec.*, N. Y., 1913, lxxxiv, 981-84.

Lewin, C.—"Ausscheidung der aromatischen Substanzen (Phenol, Indican, aromatische Oxysäuren) in Urin von Krebskranken," Beitr. z. wissensch. *Med. u. Chir.*, Festschr., Ernst Salkowski., Berl., 1904, pp. 225-238.

Lewin, C.—"Experimentelle Beiträge zur Morphologie und Biologie bösartiger Geschwülste bei Ratten und Mäusen," *Ztschr. f. Krebsf.*, 1908, Vol. VI, Hft. 2.

Lewin, Carl.—"Immunisierungs und Heilversuche mit Autolysaten bei Rattentumoren," *Ztschr. f. Krebs.*, 1911-12, xi, p. 317.

Lewin, Carl.—"Ueber Immunnisierung mit Blutserum von spontangeheilten Tumorratten" (Nullerratten), *ibid.*, p. 335.

Lewin, Carl.—"Die Enstehung histologisch neuartiger Geschwültse nach der Impfung von Tumoren bei Tieren (mit 9 Textfiguren)," *ibid.*, p. 340.

V. Leyden, E.—"Ueber die parasitäre Theorie in der Aetiologie der Krebse," *Berl. klin. Woch.*, 1905.

Lichtwitz.—"Ueber einem Fall von Sarkome der Dura mater und über dessen Beziehung zu einem vorangegangenem Trauma," *Virchow's Arch.*, 1903, Vol. CLXXIII, 2, p. 380.

Linstedt, F.—"Gibt es eine vermehrte Disposition für Karzinomentwicklung während der Gravidität?" *Deutsch. med. Woch.*, 1911, xxxvii, 1079-1081.

Loeb, L.—"Further Investigations in Transplantation of Tumors," *Jour. Med. Res.*, 1902, viii.

Loeb, Leo.—"Ueber Transplantation von Tumoren," *Virchow's Arch.*, Vol. CLXXII, p. 345.

Loeb, L.—"Cell Implantation in the Production of Tumors," *Jour. Am. Med. Assn.*, Chicago, 1903, xl, 974-977.

Loeb, L., and Leopold, Samuel.—"On the Difference in the Results Obtained after Inoculation of Tumors into the Individual in Which the Tumor Had Developed Spontaneously, and into Other Individuals of the Same Species," *Jour. Med. Res.*, 1907-8, n.s., xii, p. 299.

Loeb, L.—"Ueber Sarkomentwicklung bei einem drüsenartigen Mäuse-Tumor," *Berl. klin. Woch.*, 1906, No. 24.

Loeb, L.—"Ueber einige Probleme der experimentelle Tumorforschung," *Ztschr. f. Krebsf.*, 1907, v, p. 451.

Loeb, L.—"On Some Conditions of Tissue Growth, Especially in Culture Media," *Science*, N. Y., 1911, n.s., xxxiv, 414.

Loeb, L.—"Histogenesis of Multiple Carcinoma of the Skin," *Jour. Med. Res.*, Boston, 1913, xxviii, 235-241, 4 pls.

Loeb, L.—"Intravenous Injection of Various Substances in Animal Cancer," *Jour. Am. Med. Assn.*, Chicago, 1913, lx, 1857; also, *Interstate Med. Jour.*, St. Louis, 1913, xx, 569.

Loewenthal, W., und Michaelis, L.—"Ueber den Krebs der Mäuse (Die Histogenese der Impftumoren)" (2d paper), *Ztschr. f. Krebsf.*, 1906, iv, 639.

Löwenstein.—"Der ätiologische Zusammenhang zwischen Trauma und Sarkom, *Bruns' Beitr. z. klin. Chir.*, Vol. XLVIII.

Löwenstein, S.—"Zur Frage der 'Unfall und Krebskrankheit,'" *Monatsh. f. Unfallheilk.*, Leipzig, 1913, xx, 52-54.

Maffei, A.—"Le rôle des traumatismes dans l'étiologie des tumeurs malignes," *Jour. de Chir.*, et Ann. Soc. Belge de Chir., Brux., 1905, v, 62-67.

Marchand.—"Zur Kenntnis der Ovarialtumoren," Halle, 1879.

Marie, Pierre, et Clunet, Jean.—"Variations morphologiques d'un épithélione mammaire kystique chez la souris, au cours de transplantation en série: Transformations successives en épithéliome atypique, tumeur mixte, sarcome fuso-cellulaire," Bull. de l'assoc. Franç. pour l'étude du cancer, 1910, iii, 367-403.

Marie, Pierre, et Clunet, Jean.—"Fréquence des métastases viscérales chez les souris cancéreuses après ablation chirurgicale de leur tumeur," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, iii, 19; also, *ibid.*, pp. 348-367.

Marie, Pierre.—"Nouveau cas de tumeur maligne provoquée par une radiodermite expérimentale chez le rat blanc," Abstr. in *Arch. de l'électric. méd.*, 1911, xix (Pt. 2), p. 339.

Mattsche, Theodor.—"Ueber das Vorkommen von Carcinom auf der Basis von Lupus und Geschwüren," Göttingen.

Mayo, W. J.—"Grafting and Traumatic Dissemination in the Course of Operation for Malignant Disease," *Jour. Med. Assn.*, Chicago, 1913, lx, 512.

Medigreceanu, F.—"Ergebnisse eines Fütterungsversuches bei Ratten, die überimpfte Tumoren trugen," *Berl. klin. Woch.*, 1910, No. 17, p. 772.

Medigreceanu, F.—"On the Relative Sizes of the Organs of Rats and Mice Bearing Malignant New Growths," Proc. Roy. Soc. B., 1910, Vol. LXXXII.

Medigreceanu, F.—"Ueber die grössenverhältnisse einiger der wichtigsten Organe bei tumortragenden Mäusen und Ratten," *Berl. klin. Woch.*, 1910, No. 13.

Menétrier.—Des états morbides précancéreuses et de la formation du cancer à leur dépens," Bull. de l'assoc. franç. pour l'étude du cancer, 1908, xxviii (Suppl., pp. 29-57).

Menétrier, P., et Clunet, J.—"Données fournies par l'expérimentation sur la nature et la pathologie des cancers; Rapport présenté au premier congrès internat. de pathol. comparée," Paris, Oct. 17-23, 1912, Bull. de l'assoc. franç. pour l'étude du cancer, 1912, v, 239.

Meyer, A. W.—"Experimentelle Epithelwucherungen," *Ziegler's Beitr. z. pathol. Anat. u. allg. Pathol.*, 1909, Vol. XLVI, Hft. 3.

Michaelis, Leonor.—"Ueber den Krebs der Mäuse" (first paper), "Herkunft, Bau, und klinische Erscheinungen der Geschwülste; ihre Uebertragbarkeit," *Ztschr. f. Krebsf.*, 1906, iv, 1.

Mitchell, Charles.—"The Philosophy of Tumor Disease: A Research for Principles of Treatment," 1890, xi, 263.

Moore, C. H.—"The Antecedents of Cancer," *Brit. Med. Jour.*, Aug. 12 and 26, 1865, pp. 164, 201, 677.

Moore, Charles H.—"On the Influence of Inadequate Operations on the Theory of Cancer," Trans. Roy. Med.-Chir. Soc., London, 1867, 2s., Vol. XXXII, p. 245. See also: Trans. Path. Soc. of London, Vol. XXV, 1874.

Moore, Charles H.—"On the Influence of Inadequate Operations on the Theory of Cancer," Medico-Chirurgical Trans., 1867, Vol. L, p. 24; also, "Discussion on Cancer," May 7, 1874, Trans. Path. Soc. of London, 1874, Vol. XXV, p. 287.

Morau, H.—"Recherches expérimentelles sur la transmissibilité de certains néoplasmes (épithéliomes cylindriques), *Arch. de méd. expér. et d'anat. path.*, Paris, 1894, vi, 677-705, 1 pl.

Morau and Jensen's "Tumor," *The Lancet*, Dec. 1, 1906, p. 1544.

Morgan C. de.—"Discussion on Cancer," Trans. Path. Soc. of Lond., 1874, Vol. XXV, pp. 287, 387.

Morris (Sir), Henry.—"The Bradshaw Lecture on Cancer and Its Origin" (delivered before the Roy. Coll. of Surgeons of England, on Dec. 9, 1903), *The Lancet*, London, Dec. 12, 1903, Vol. II, p. 1633.

Morris (Sir), Henry.—"Morau and Jensen's Tumor" (letter), *The Lancet*, London, Nov. 24, 1908.

Moullin, C. W. Mansell.—"The Bradshaw Lecture on the Biology of Tumours," delivered at the Roy. Coll. Phys. and Surg. of England, on Thursday, Dec. 5, 1912, London, 1913.

Murphy, I. B.—"Transplantability of Tissues to the Embryo of Foreign Species," *Jour. of Exp. Med.*, 1913, p. 482.

Murray, J. A.—"Studies on the Heredity of Cancer in Mice," 17th Internat. Congr. of Med., Lond., Aug. 6, 1913, iii, p. 67.

Nadal, Pierre.—"Quelques particularités de propagation d'un cancer du sein," Bull. de l'assoc. franç. pour l'étude du cancer, 1911, iv, 42.

Nadal, Pierre.—"Encore le 'Périthéliome.' Tumeurs périthéliales ou aspects périthéliaux?" Bull. de l'assoc. franç. pour l'étude du cancer, 1911, iv, p. 156.

Nichols, Ed. H.—"Implantation of Tissue and Its Relation to Cancer," *Jour. Med. Res.*, Boston, 1904-5, n.s. 8, p. 187.

Nichols, E. H.—"Implantation of Tissue and Its Relation to Cancer." Third Report, Harvard Cancer Commission, 1905.

Oberndorfer, S.—"Tumor und Trauma," *Aertzl. Sachverständl.-Ztg.*, 1907.

Oberndorfer.—"Appendixtumoren," *Ergebn. d. allg. Pathol. u. pathol. Anat.*, 1909, xiii, pp. 585-592. Discussion, *Verhandl. d. Deutsch. pathol. Gesell.*, Erlangen, 1910.

Oertel, Horst.—"On the Histogenesis of Tumors, Particularly Cancer," *New York Med. Jour.*, July 6, 1907, LXXXVI, 14-21.

Orth.—"Die Morphologie der Krebse und die parasitäre Theorie," *Berl. klin. Woch.*, 1905, No. 11.

Orth, J.—"Präcarcinomatöse Krankheiten und künstliche Krebse," *Ztschr. f. Krebsf.*, 1910-11, x, p. 42.

Orth, J.—"Ueber die Krebsgeschwülste des Menschen: Sitzung ber. der kgl. preuss. Akademie d. Wissensch.," Jan. 28, 1909, 107; "Ueber einige Krebsfragen," *ibid.*, Dec. 1909, p. 1225; "Präcarcinomatöse Krankheiten und künstliche Krebse," *Ztschr. f. Krebsf.*, 1910, Vol. X, No. 5, p. 42.

Paget, Sir James.—"Lectures on Surgical Pathology," London, 1853.

Paget, Sir James.—"The Morton Lecture on Cancer and Cancerous Diseases," *Lancet*, November 19, 1887.

Park, Roswell.—"The Nature of the Cancerous Process," II Cong. Int. de Chir., Brux., Sept. 21-25, 1908, Vol. II, p. 321 (Reports).

Petersen.—"Anatomische und klinische Untersuchungen über den Magen und Darmkrebs," vortrag auf dem 32 Kongr. der deutsch. Ges. f. Chir., Berlin, 1903.

Petersen, W., und Colmers.—"Anatomische und klinische Untersuchungen über die Magen und Darmcarcinome," Beitr. z. klin. Chir., Vol. XLIII, Hft. 1.

Pietro, E.—"Sull azione del succio dei tumori maligni sovra l'emoglobina del sangue," *Chir. med. ital.*, Milano, 1903, xlii, 693-699.

Petit, G.—"Premières recherches sur le sérum d'une chatte atteinte de cancer de la mamelle," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, iii, 305.

Plimmer, H. G.—"On the Etiology and Histology of Cancer," *Practitioner*, Lond., 1899 (Special Cancer number), lxii, 4, p. 430.

Podwyssozki, W.—"Ziegler's Beiträge zur path. Anat.," 1886.

Podwyssozki, W.—"Neuere Ansichten zur Begrundung der Reiztheorie des Krebses und der bösartigen Geschwülste," *Ztschr. f. Krebsf.*, 1908-1909, vii, p. 286. An address at the Initiatory Session of the Internat. Assoc. for Cancer Res., May 23, 1908, in Berlin.

Podwyssotzsky, W.—"Ueber Erzeugung tumorartige Wucherungen der Gewebe mittelst mechanische Reize." Report of the Wissensch.

Abt. d. Russ. Gesell. zur Bekämpfung des Krebses (Sess. of Apr. 21, 1909), *Ztschr. f. Krebsf.*, 1910, ix, p. 65.

Power, D'Arcy.—"Some Effects of Chronic Irritation upon Living Tissues, Being First Steps in a Rational Study of Cancer," *Brit. Med. Jour.*, 1893, ii, pp. 830-834 (61st Ann. Meeting of the Brit. Med. Assoc., Newcastle-on-Tyne, Aug. 1, 2, 3, and 4, 1873, Sect. of Pathology).

Quadrio, Giuseppe Maria.—"Nuovo metodo per curare sicuramente ogni canchero coperto e specialmente le ghiande scirrhose delle mamelle e di altre parti del corpo," Venezia, 1750.

Remak, Robert.—"Ueber die Entwicklung der Geschwülste," *Deutsche Klinik*, 1854, No. 19.

Ranvier, L. A., et Cornil, V.—"Contribution à l'étude du développement histologique des tumeurs épithéliales" (Cancroide), Paris, 1866.

Ribbert, Hugo.—"Carcinom und Tuberculose," *Münch. med. Woch.*, 1894, xli, 321-4.

Ribbert, Hugo.—"Die Enstehung der Geschwülste," *Deutsch. med. Woch.*, 1895.

Ribbert, Hugo.—"Histogenese des Carcinoms," *Virchow's Arch.*, 1894, Vol. CXXXV, and 1895, Vol. CXLI.

Ribbert, Hugo.—"Die neuere Untersuchungen über Krebsparasiten," *Deutsch. med. Woch.*, 1894, xx, 339-343.

Ribbert, H.—"Das pathologische Wachstum," Bonn, 1896.

Ribbert, Hugo.—"Geschwülstelehre für Aerzte und Studierende," Bonn, 1904.

Ribbert, Hugo.—"Ueber Transplantation auf Individuen anderer Gattung," Verhandl. d. Deutsch. path. Gesell., 1904, Jena, 1905, viii, 104-109.

Ribbert, Hugo.—"Ueber primäre Tuberculose und Anthrakose der Lungen," *Deutsch. med. Woch.*, 1906, xxxii, 1615-1617.

Ribbert, Hugo.—"Zur Kenntnis des Carcinoms," *Deutsch. med. Woch.*, Leipz. u. Berl., 1906, xxxii, 1693.

Ribbert, H.—"Beiträge zur Enstehung der Geschwülste—ein kritische Besprechen von D. von Hansemann," *Ztschr. f. Krebsf.*, 1907, Vol. V, 522.

Ribbert, H.—"Die Enstehung des Carcinoms" (Beiträge zur Entstehung der Geschwülste, zweite Ergänzung.), Bonn, 1907.

Ribbert, H.—"Das Wesen der Krankheit," Bonn, 1909.

Ribbert, Hugo.—"Das Karzinom des Menschen, sein Bau, sein Wachstum, sein Entstehung," Bonn, 1911.

Roger.—"Toxicité des extraits de tissus normaux," Compt. rend. soc. de biol., Paris, 1891, 9 s., iii, 727-729.

Rohdenburg, George L.—"The Effects of Chronic Irritation on Tissues," Crocker Spec. Res. Fund, 1913, Vol. III, p. 75.

Röpke, W.—"Die Bedeutung des Traumas für die Enstehung der Carcinome und Sarkome," *Arch. f. klin. Chir.*, 1905-6, Vol. 78, p. 201.

Rössle, R.—"Bemerkungen zur Ätiologie der Geschwülste," *Deutsch. med. naturf. Gesell.*, Jena, 1904.

Rössle, R.—"Der Pigmentierungsvorgang im Melanosarkom," *Ztschr. f. Krebsf.*, 1904, Vol. II, p. 291.

Rössle, R.—"Die Rolle der Hyperämie und des Alters in der Geschwülstenstehung," *Münch. med. Woch.*, 1904, 51.

Rous, Peyton, and Murphy, I. B.—"The Nature of the Filterable Agent

Causing a Sarcoma of the Fowl," *Jour. Am. Med. Assoc.*, June 22, 1912, Vol. lviii, 1938.
Roussy, Gustave, et Ameuille, Pierre.—"À propos du 'Perithéliome'—Aspects périthéliaux dans les tumeurs épithéliales," Bull. de l'assoc. franç. pour l'étude du cancer, 1911, iv, 29 (Sess. of Jan. 16, 1911); also, *ibid.*, p. 143.
Russell, B. R. G.—"The Manifestation of Active Resistance to the Growth of Implanted Cancer." Fifth Scientific Report of the Imperial Cancer Research Fund, London, 1912.
Sanfelice, Francesco.—"Ueber die Wirkung der löslichen Produkte der Blastomyceten in Bezug auf die Aetiologie der malignen Geschwülste," *Ztschr. f. Krebsf.*, 1907-8, Vol. VI, 166.
Sanfelice, F.—"Sugli epitheliomi perianali del cane e sulla metaplasia che essi presentano in seguito all azione del siero antcancerigno," *Ann. di oncol. speriment.* Torino, 1912, i, pp. 73-183.
Schöne, G.—"Untersuchungen über Karzinomimmunität bei Mäusen," *Münch. med. Woch.*, 1906, liii, 2517.
Schöne, G.—"Untersuchungen über Geschwülstimmunität bei Mäusen," Verhandl. der deutschen Gessellsch. f. Chirurgie, 1907, xxvi, 866.
Schöppler, Herrmann.—"Einmaliges Trauma und Carcinoma," *Ztschr. f. Krebsf.*, 1910-11, x, p. 219.
Seeligmann.—"Mitteilungen über Studien zur Erforschung und Heilung des Krebses beim Menschen," *Wien. klin. Rundschau,* 1903, xvii, p. 43.
Senn, N.—"Biology of Tumors," *Med. Register,* 1887.
Sobré-Casas, C. (Buenos Aires).—"Les théories pathogéniques du cancer," *Tribune méd.*, Paris, 1908, n. s., vi. 262-265.
Slye, Maud.—"The Incidence and Inheritability of Spontaneous Cancer in Mice" (Preliminary Rep.), *Ztschr. f. Krebsf.*, 1913, p. 500.
Sticker, Anton.—"Transplantables Rundzellensarkom des Hundes," *Ztschr. f. Krebsf.*, 1906, Vol. IV, 227.
Sticker, A.—"Die Immunität und die spontane Heilung der Krebskrankheit nach den Ergebnissen der modernen experimentellen Forschung," *Zeitschr. f. Krebsf.*, 1909, vii, 55.
Taentscher, K.—"Ueber Krebsforschung und Krebshandlung," *St. Petersburger med. Woch.*, 1908, No. 46.
Theilhaber, A.—"Zur Aetiologie der Myome und Carcinome des Uterus," *Ztschr. f. Krebsf.*, 1909-10, viii, p. 546.
Theilhaber, A., und Greischer, S.—"Zur Aetiologie der Carcinome," *Ztschr. f. Krebsf.*, 1910, ix, p. 530; Résumé by Theilhaber, A., p. 549.
Theilhaber und Theilhaber, F.—"Zur Lehre vom Zusammenhang von Krebs und Narbe," *Ztschr. f. Krebsf.*, 1910, ix, p. 554.
Thiersch, Carl.—"Der Epithelialkrebs, namentlich der Haut. Eine anatomisch-klinische Untersuchung. Mit einen Atlas microscopischer Abbildungen," Leipz., 1865.
Tisenhausen, M.—"Zur Frage der Transplantation von Embryonalgewebe," *Russky Wratsch,* 1908, No. 25.
Tsunoda, T. (Kyoto).—"Ueber die Histogenese des multiplen beginnenden Magenkrebses," *Ztschr. f. Krebsf.*, 1910, ix, p. 436. (From the city Virchow Hosp., Berl., v. Hansemann.)
Turnbull, Arthur.—"On the Genesis of Cancer—Preliminary Communication," *Brit. Med. Jour.*, Oct. 11, 1913, ii, p. 905.
Tyzzer, E. E.—"A Series of Spontaneous Tumors in Mice, with Ob-

servations on the Influence of Heredity on the Frequency of Their Occurrence," *Jour. Med. Res.*, Oct., 1909, xxi, No. 3, p. 479.

Tyzzer, E.—"A Study of Inheritance in Mice, with Reference to Their Susceptibility to Transplantable Tumors," *Jour. Med. Res.*, Oct., 1909, xxi, 519.

Uhlenhuth, Haendel, and Steffenhagen.—"Ueber Immunität bei Rattensarkom," *Centralbl. f. Bact.*, 1910, Erst Abt, xlvii, 465.

Vaughan, John W.—"Sensitization in Cancer," *New York Med. Jour.*, May 21, 1910.

Vaughan, V. C., and Novy, Frederick G.—"Cellular Toxins, or the Chemical Factors in the Causation of Disease," 4th ed., Phila. and New York, 1902.

Vidal, E.—"Influence de l'état physico-chimique de l'antigène sur la teneur en sensibilisatrices du sang des animaux injectés de cancer épithélial," Bull. de l'assoc. franç, pour l'étude du cancer, 1910, iii, 254-267.

Vidal, E.—"Sarcome polymorphe spontane transmissible chez une souris immunisée par trois greffes de cancer épithélial," Bull. de l'Assoc. franç. pour l'étude du cancer, 1911, iv, 61-70 (Sess. of Feb. 20, 1911).

Virchow, R.—"Die krankhaften Geschwülste," Berl., 1863, Vol. II, Onkologie, Pt. 1.

Virchow, Rudolph.—"Die Krankhaften Geschwülste," 1864-5, Vol. III, Onkologie.

Waldeyer, W.—"Die Entwicklung der Carcinome," *Virchow's Archiv*, 1867, Vol. XLI, No. 24, p. 470, *ibid.*, Vol. LV, 1872, p. 67.

Waldeyer, W.—"Ueber den Krebs," *Volkmann's Sammlung klinischer Vorträge*, 1872, No. 33 (Chir. No. 10), 163-196.

Walker, C. E.—"Theories and Problems of Cancer," *Science Prog.*, 20th Century, London, 1911-12, vi, 670; 1912, vii, 104, 223.

Walker, C. E., and Whittingham, H. E.—"Results of Complete Removal by Operation of Transplanted Mouse Cancer," *Lancet*, 1912, ii, 1357.

Walshe, Walter Hayle.—"The Nature and Treatment of Cancer," London, 1846.

Wells, H. Gideon.—"The Resistance of the Human Body to Cancer," *Jour. Am. Med. Assn.*, May 29, 1909, lii, p. 1731.

Wells, H. G.—"The Purines and Purin Enzymes of Tumors," Tr. Chicago Path. Soc., 1911-12, viii, 250; also, Proc. Am. Soc. Biol. Chemists, Balt., 1911.

White, Charles Powell.—"The Pathology of Growth, Tumours," London, 1913.

Williams, W. R.—"Gall-stones and Cancer," *The Lancet*, Lond., 1896, ii, 1187.

Williams, W. R.—"The Question of the Origin of Malignant from Non-Malignant Uterine Neoplasms," *Ann. Surg.*, Phila., 1896, xxix, 257-264.

Williams, W. R.—"The Rôle of 'Rests' in the Origin of Tumors," *Med. Press and Circ.*, Lond., 1896, n.s., lxii, 179.

Woglom, W. H.—"Mice Immunized Subcutaneously Are Resistant to the Implantation of Cancer in Internal Organs," *The Lancet*, July 8, 1911.

Woglom, W. H.—"Contributions to the Theory of the Individuality of Carcinoma," Crocker Spec. Res. Fund, 1913, Vol. III, p. 137.

Woglom, W. H.—"The Study of Experimental Cancer," Columbia University Press, New York, 1913.

Zenker, H.—"Der primäre Krebs der Gallenblase und seine Beziehung zu Gallensteinen und Gallensteinnarben," *Deutsch. Arch. f. klin. Med.*, Leipz., 1888-9, xliv, 150-184.

Zimmer, A.—"Soll die anatomische Form eines Rektumcarcinoms bestimmend sein für seine Operabilität?" *Wien. klin. Woch.*, 1909, No. 35.

CLINICAL COURSE

(INCLUDING SPONTANEOUS CURE)

DIAGNOSIS—POSSIBLE ERRORS IN DIAGNOSIS

Abderhalden, E., und Suwa, A.—"Weiterer Beitrag zur Kenntnis der bei partiellen Hydrolyse von Proteinen auftretende Spaltprodukte," *Ztschr. f. physiol. Chem.*, 1910, LXVI, pp. 13-18.

Abderhalden, E., und Pincussohn, L.—"Zur Kenntnis der peptolytische Fermente verschiedenartiger Krebse und anderer Tumoren—4 Mitteilung," *Ztschr. f. physiol. Chemie*, Strassb., 1910, lxvi, 277-283.

Abderhalden, E.—"Weiterer Beitrag zur Kenntnis der beider partiellen Hydrolyse von Proteinen auftretenden Spaltprodukten," *Ztschr. f. physiol. Chem.*, Strassb., 1910, 417-419; also, "Notiz zum Nachweis peptolytischer Fermente in Tier und Pflanzengeweben," *ibid.*, lxxvi, 137-139.

Abderhalden, E.—"Neue Forschungsrichtungen auf dem Gebiete der Störungen des Stoffwechsels," *Arch. f. Wissensch. u. prakt. Tierh.*, Berl., 1910, xxxvi, Suppl. Bd., I-VII.

Achard, Ch., Benard, Henri, et Gagneux, Ch.—"Leucodiagnostique du cancer," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, iii, 66-81; also, *ibid.*, 209.

Bainbridge, W. S.—"Three Unique Head Tumors: I. Indurated Mass in Scalp, Simulating Malignancy, Caused by Foreign Body. II. Epithelioma of Scalp. III. Intracranial Tumor, *N. Y. Polyclin. Jour.*, Apr., 1909.

Bainbridge, W. S.—"Possible Errors in the Diagnosis of Abdominal Cancer—A Plea for Exploratory Laparotomy—Illustrative Cases," *N. Y. State Jour. of Med.*, Oct., 1913.

Barrett, C.—"Ueber Komplementablenkung bei Menschencarcinom," *Zeitschr. f. Krebsf.*, Berlin, xi, 1911, p. 245.

Broca.—"De la propagation de l'inflammation des tumeurs dites cancéreuses," Paris.

Beatson, (Sir) George Thomas.—"Cachexia in the Diagnosis of Malignant Disease," Glasgow Obst. and Gynec. Soc., Nov. 25, 1896.

Beatson, (Sir) George Thomas.—"Local Recurrence after Removal as a Sign of Malignancy in Tumors of the Female Mamma," *Edin. Med. Jour.*, June, 1910.

Beatson (Sir) George Thomas.—"Splenic Metastasis in a Case of Carcinoma of Tongue, Due Probably to Vascular Dissemination," *Glasgow Med. Jour.*, 1912, lxxvii, 161-168, 3 pls.

V. Bergmann, A.—"Differentialdiagnose der Abdominaltumoren," *St. Petersb. med. Woch.*, 1909, No. 5.

Boas, Israel.—"Beiträge zur Kenntnis der Rektumcarcinome nebst Bemerkungen zur Frühdiagnose," *Arch. f. Verdauungskr.*, Vol. II.

Bolognesi, J.—"Spontan Zurückbildung von Hautepitheliome," *Arch. f. klin. Chir.*, 1910-11, xciv, 705.

Caan, A.—"Ueber Komplementablenkung bie Karzinom," *Münch. med. Woch.*, April 4, 1911.

Cathcart, C. W.—"The Essential Similarity of Innocent and Malignant Tumours—A Study of Tumour Growth," Bristol, 1897.

Clairmont, Paul.—"Einige Fälle von seltenen Geschwülstmetastasen," *Arch. f. klin. Chir.*, 1909, lxxxix, p. 512.

Coley, W. B.—"Myositis ossificans traumatica: A Report of Three Cases Illustrating the Difficulties of Diagnosis from Sarcoma," *Ann. of Surg.*, Phila., March, 1913.

Delbet, Pierre.—"Épithéliome pavimenteux—Transformation de cellules épithéliales en cellules cancéreuses (1 planche hors texte)," Bull. de l'assoc. franç. pour l'etude du cancer, 1910, iii, 325.

Delbet, Pierre.—"Leucodiagnostique du cancer" (note de M. Gagneux, etc.), Bull. de l'assoc. franç. pour l'étude du cancer (Sess. of Mar. 14, 1910); 1910, iii, 119-126.

Von Dungern und Halpern.—"Ueber komplementsbindungreaktion mit Liquor cerebrospinalis bei Karzinom," *Münch. med. Woch.*, 1913, lx, 1923.

Foerster, A.—"Wassermann Reaction in Relation to Cancer," *Lancet*, June 24, 1911.

Fox, Frederick J.—"The Wassermann Reaction in Cancer," *Medical Record*, New York, August 16, 1913.

Fuhs, Jacob, and Lintz, Wm.—"The Diagnostic Significance of the Urinary Methylene-blue Reaction, with Special Reference to Malignancy," *Jour. Am. Med. Assn.*, June 24, 1911, p. 1882.

Gaylord, Harvey R., and Clowes, George H. A.—"On Spontaneous Cure of Cancer," *Surg. Gyn. and Obst.*, June, 1906, Vol. II, No. 6.

Gleitsmann, Joseph William.—"Remarks on the Spontaneous Disappearance of Malignant Growths," *Med. Rec.*, N. Y., Apr. 22, 1911.

Greenwald, Isidor.—"The Reaction of Salomon and Saxl as a Diagnostic Test for Carcinoma," *Arch. Intern. Med.*, 1913, xii, p. 283.

Guinard, A.—"Cancer du sein; fibromes de l'utérus: castration subtotal et disparition consécutive de la tumeur du sein," Bull. et Mém. Soc. chir. de Par., 1904, n.s., xxx, 29-34.

Von Hansemann.—"Das gleichzeitige Vorkommen verschiedenartiger Geschwülste bei denselben Person," *Ztschr. f. Krebsf.*, Jena, 1904, i, 183-198.

Heimann, F.—"Serodiagnosis of Cancer (Erfahrung mit der aberhaldenschen Fermentreaktion bei Carcinom)," *Berl. klin. Woch.*, Apr. 7, 1913, l, No. 14.

Henke, Friedrich.—"Mikroscopische Geschwulstdiagnostik. Praktisch Anleitung zur Untersuchung und Beurtheilung der in Tumorform auftretenden Gewebswucherungen. Für Studierende und Aerzte, besonders auch Specialaerzte.," Jena, 1900.

Hirsch, Franz.—"Ueber Carcinom-Recidiv., *Inaug.-Diss.*, Freiburg im Br., 1908.

Janeway, Henry W.—"The Serum Reaction in Cancer," *Ann. of Sur.*, Jan., 1909, xlix, p. 27.

Jessup, D. S. D.—"Hodgkin's Disease Involving the Uterus," *Am. Jour. of Obstet. and Dis. of Women and Children*, Vol. LXVI, No. 3, 1913.

Kaldeck, Rudolf.—"Ueber die Salomon-Saxl'sche Schwefelreaktion im Harne Krebskranker," *Wien. med. Woch.*, 1911, lxii, p. 1681.

Koster, W.—"Spontanheilung einer als Sarcoma orbitae diagnostizierten Geschwulst," *Ztschr. f. Augenheilk.*, Jan., 1908, Vol. XIX.
Kraus, Fr.—"Diffuse Verkalkung in cicatrisirenden Leberkrebsen," *Prag. med. Woch.*, 1885.
Kromer, P.—"Ueber Schwierigkeiten bei der Diagnose von Abdominaltumoren," Mitteil. aus d. Grenzg. d. Med. u. Chir., 1907, Vol. xviii, Hft. 3, 441.
Kuttner, L.—"Zur Diagnose der Rektumcarcinome," *Ztschr. f. Krebsf.*, 1908-9, p. 351.
Lazarus-Barlow.—"The Precipitin Reaction in Malignant New Growths," Archives Middlesex Hosp. (Cancer Res.), 1906, v. 27.
Levin, S.—"Cancer and a Plea for Earlier Diagnosis," *Jour. Mich. Med. Soc.*, Grand Rapids, 1914, xiii, 27-30.
Lowy, Otto.—"A Serum Reaction as an Aid in the Diagnosis of Cancer," *Jour. Am. Med. Assn.*, Feb. 7, 1914.
Mohr.—"Ueber spontan Heilungsvorgange des Carcinoms," *Therap. Monatschr.*, 1903.
Murachi, Nagataka.—"Zur Kenntnis des Schwefelstoffwechsels der Krebskranken," *Biochem. Ztschr.*, 1912, p. 138.
Nadal, Pierre.—"Embryome de l'ovaire. Dégénérescence maligne monotissulaire," Bull. de l'assoc. franç. pour l'étude du cancer, 1912, v. 189 (Sess. of Nov. 18, 1912).
Newmark, L.—"The Occurrence of a Positive Wassermann Reaction in Two Cases of Non-Specific Tumors of the Central Nervous System," *Jour. Am. Med. Assn.*, June 6, 1912, p. 11.
Offergeld.—"Die Beteiligung des hämatopoetischen Systems an der Metastasierung beim Uteruscarcinom," *Ztschr. f. Geburtsh. u. Gynäk.*, Vol. LXIII, Hft. 2.
Offergeld.—"Die Metastasen in der Bauchhohle bei Uteruscarcinom," *Arch. f. Gynäk.*, 1908, Vol. LXXXVII, p. 298.
Offergeld.—"Das Uteruscarcinom und seine Metastasen in Pleura und Lungen," *Arch. f. Gynäk.*, 1909, Vol. LXXXVII, p. 286.
Offergeld.—"Hautmetastasien beim Uteruscarcinom," *Monatsschr. f. Geburtsh. u. Gynäk.*, Vol. XXIX, Ergänzungshft.; also, "Ueber seltene Metastasien des Uteruscarcinoms," *Monatsschr. f. Geburtsh. u. Gynäk.*, Vol. XXIX, Hft. 2.
Orth, J.—"Ueber Heilungsvorgange an Epitheliomen nebst allgemeinen Bemerkungen über Epithelioma," *Ztschr. f. Krebsf.*, 1903-4, i, 399.
Orth, J.—"Ueber Heilungsvorgange an Epitheliomen nebst allgemeinen Bemerkungen über Epitheliome," *Ztschr. f. Krebsf.*, 1904, Hft. 5, p. 399.
Petersen, Otto V. C. E.—"Untersuchungen über den Wert von Saxl Schwefelreaktion bei Karkinom in der Verdauungsorganen," *Deutsch. med. Woch.*, 1912, xxxviii, No. 33, p. 1536.
Pinkuss, A.—"Weitere Erfahrungen über serologische Diagnostik Verlauf u. Behandlung des Karzinoms," *Deut. med. Woch.*, xxxviii, 1912.
Pribram, Egon, Ewald.—"Ueber das Vorkommen des Neutralschwefels im Harn und seine Verwendung zur Karkinomdiagnose," *Wien. klin. Woch.*, 1911, xxiv, No. 35, p. 1235.
Rodman, William L.—"The Early Diagnosis of Cancer of the Breast and Best Operative Technic," *Penn. Med. Jour.*, 1909, Vol. XIII, No. 2, p. 100.
Rosenberg, M.—"Zur Frage der Serologischen Karzinomdiagnostik," *Deut. med. Woch.*, xxxviii, 1912.

Rothacker, Alfons.—"Zur Frage der Carcino-Sarkome; Carcino-Sarkombildung in einem papillären, multilokulären Adenocystom," *Ztschr. f. Krebsf.*, 1912-13, Vol. XII, p. 39.

Salkowski, E.—"Ueber die Verwertung des Harnbefundes zur Carcinomdiagnose," II., *Berl. klin. Woch.*, 1910, xlvii, p. 1746.

Salkowski, E.—"Ueber die Verwertung des Harnbefundes zur Carcinomdiagnose," III: Nach Versuchen von Dr. Kenji Koho aus Tokio, *Berl. klin. Woch.*, 1910, xlvii, p. 2297.

Salkowski and Kojo.—"Ueber die Ververtung des Harnbefundes sur Carcinomdiagnose," III, *Berl. klin. Woch.*, 1910, xlvii, p. 2297.

Salomon, Hugo, und Saxl, Paul.—"Eine Schwefelreaktion im Harne Krebskranker," *Wien, klin. Woch.*, 1911, xxiv, No. 13, p. 449; *Deutsch. med. Woch.*, 1912, xxxviii, p. 53.

Stammler.—"Ueber neuere Methoden der serologischen Krebsdiagnose," *Arch. f. klin. Chir.*, 1911, 96, 158.

Theilhaber, A., und Edelberg, H.—"Zur Lehre von der spontanen Heilung der Myome und Carcinome," *Ztschr. f. Krebsf.*, 1913, 13, pp. 461-499. With plate.

Theilhaber, A., und Edelberg, H.—"Zur Lehre von der spontan Heilung der Myome und Carcinome," *Ztschr. f. Krebsf.*, 1913, 13, p. 461.

Theilhaber, A.—"Können Karzinom spontan heilen?" *Deutsch med. Woch.*, 1913, xxxix, 1314.

Tuffier.—"Des abcés profonds de l'abdomen comme premier symptome d'un cancer de l'intestin," *Sem. méd.*, Paris, 1904, xxiv, 193.

Verbrycke, J. Russell, Jr.—"Methylene Blue Test in Urine of Cancer Patients," *Med. Rec.*, Oct. 28, 1911, Vol. LXXX, p. 876.

Weinstein, J. W.—"The new Test for Cancer of the Stomach. With Suggested Improvements," Crocker Spec. Res. Fund, 1913, Vol. III, p. 162.

Zangger.—"Merkwürdiges Verschwinden einer krebsartigen Geschwulst im Halse," Korresponzbl. f. Schweiz. Aerzte, 1904, No. 19.

PROPHYLAXIS—CAMPAIGN OF EDUCATION

Annis, E. J.—"Cancer: A Brief History, with some Remarks on the Prophylaxis of Cancer of the Digestive Organs," *Am. Jour. of Gastro-Enterology*, 1911-1912, i, p. 1.

Bainbridge, W. S.—"Metastasis Following Incision of a Sarcoma," *N. Y. Polyclinic Journal*, January, 1908, p. 17.

Bainbridge, W. S.—The Campaign against Cancer: Educational, experimental, and clinical, *Am. Jour. Dermat.*, 1911, v, 15.

Bainbridge, W. S.—Intestinal Stasis in relation to cancer etiology and prophylaxis, *Jour. Med. Soc. of N. J.*, 1912.

Bloodgood, Joseph Colt.—"Control of Cancer," *Jour. Am. Med. Assn.*, December 27, 1913, p. 2283.

Bloodgood, Joseph Colt.—"Diagnosis and Treatment of Border-line Pathological Lesions," *Surg. Gyn. and Obstet.*, Jan., 1914, p. 19.

Boldt, H. J.—"How May we Reduce the Mortality from Cancer of the Uterus? With Special Reference to Treatment and to Publicity through the Lay Press," *Jour. Am. Med. Assn.*, March 19, 1913, p. 968.

Councilman, W. T., and Magrath, G. B.—"The Lesions of the Skin and the Tumor Formations in Xeroderma Pigmentosum," Fifth Report of the Cancer Commission of Harvard University, 1909.

Crile, George W.—"The Cancer Problem," *Jour. Am. Med. Assn.*, June 6, 1908.
Henson, W. Warner.—"Cancer in Kafirs; Suggested Cause," *Guy's Hospital Gazette*, March 26, 1904.
Keen, W. W.—"The Danger of Allowing Warts and Moles to Remain Lest they Become Malignant," *Jour. Am. Med. Assn.*, xliii, 1904, p. 96.
Sachs, E.—"Die Wintersche 'Bekämpfung des Gebärmutterkrebses'—Eine historich-kritische Studie." Presented to the II. Int. Konfer. für Krebsf., in Paris, as a supplement to Winter's paper, "Fortbildung. der Aerzte und Volksaufklärung," *Ztschr. f. Krebsf.*, 1910, IX, p. 469.
Sobré-Casas, C.—"Le Cancer. Prophylaxie—étiologie—traitement," Paris, 1902.
Syms, P.—"The Prevention and Cure of Cancer," *Med. Rec.*, N. Y., 1913, lxxxiii, 881-8.
Winter, Georg.—"Die Bekämpfung des Uteruskrebses," Stuttgart, 1904.
Winter, Georg.—"Der Erfolg der 'Bekämpfung des Uteruskrebses' in Ostpreussen," *Centralbl. f. Gynäkol.*, 1904, No. 14.

CANCER "CURES"

Adamkiewicz.—"Wiederherstellung des Sehvermögens eines durch Krebs fast verblindeten Auges mit Hilfe der Cancroinmethode," München, 1903.
Aronsohn, Ed.—"Günstige Beeinflussung eines Kehlkipfkrebses durch Anwenndung von Antimeristem," *Ztschr. f. Krebsf.*, 1910, IX, p. 367.
Bainbridge, W. S.—"Trypsin in Cancer"—A Preliminary Statement, *New York Med. Jour.*, Mar. 2, 1907.
Bainbridge, W. S.—"The Enzyme Treatment for Cancer"—Final Report, *New York Med. Jour.*, 1909; also *Med. Rec.*, July 17, 1909.
Bainbridge, W. S.—"The Enzyme Treatment for Cancer. Scientific Report on Investigations with reference to the Treatment of Cancer." Published with the authority of the Committee on Scientific Research of the New York Skin and Cancer Hospital, No. I, New York, 1909.
Balfour's Botany, 1854. (Violet Leaves.)
Ball, Walter.—"A Note on the Therapeutic Measures used in the Treatment of Cancer in the Cancer Wards during 1905," Arch. Middlesex Hosp., 1908, vii, pp. 75-78.
Beard, John.—"The Enzyme Treatment of Cancer," 1911.
"Cancer Cures" (Editorial), *British Med. Journal*, March 23, 1907, p. 703.
Clay, J.—"Notes on Chian turpentine and its use in Cancer," *The Lancet*, Lond., 1880, ii, 533-536.
Clay, J.—"Chian turpentine in Cancer," *The Lancet*, Lond., 1880, i, 696.
Clay, J.—"On the Treatment of Cancer of the female generative organs by a new method," *The Lancet*, Lond., 1880, i, 477-479.
Clay, J.—"On the use of Chian turpentine in Cancer," *The Lancet*, Lond., 1881, ii, 1033-1035.
Clay, J.—"On the Treatment of Cancer," 1882. *See also Lancet*, 1880-87.

Culpepper, Nicholas.—"The English Physician," *Reissus,* 1792. (Violet Leaves.)

"Cure of Cancer.—Report of Board appointed to Inquire into the claims made by Mr. J. A. Davis in Respect of his Alleged Remedy for Cancer. Presented to Both Houses of Parliament by His Excellency's Command," Victoria, 1911.

Doyen.—"Les traitements du cancer," *Bull. méd.,* Paris, 10, 1904, xviii, 909; also, *Presse méd.,* Par., 1904, ii, 671.

Doyen.—"Étiologie et Traitement du Cancer," Paris, 1905.

Doyen.—"Le sérodiagnostique du cancer et le rèle pathogène du Micrococcus neoformans," Bull. et mém. soc. anat. de Paris, 1905, lxx, 207-209; also, Sérodiagnostique du cancer at lésions experimentales produites par le Micrococcus neoformans, *ibid.,* 209-224; also, "Traitement du cancer par la sérothérapie et la vaccination antinéoplastiques d'après la méthode de Doyen," *Prog. méd. Belge,* Brux., 1905, vii, 81-83.

Editorial (The Enzyme Treatment), *Brit. Med. Jour.,* July 24, 1909, p. 218.

Editorial, *Lancet,* Nov. 23, 1901, p. 1430. (Violet Leaves.)

Hulke, J. W.—"Memorandum on the Results of a trial of Chian Turpentine as a reputed remedy for Cancer of the female genital organs, made during several months in the year 1880, in Whitbread Ward, Middlesex Hospital," *Lancet,* Lond., 1881, i, 1919.

Johannsen.—"Ueber drei Verreuhe der Behandlung inoperable Karzinome mit Antimeristem," *Centralblatt für Gyn.,* 1912, Vol. XXXVI, No. 14, p. 426.

Kennedy, Saml.—"Is Cancer curable? The cancer controversy: Mattei v. the knife; how it began, how it ended; with epitome of Mattei's treatment of Cancer and general diseases," London, 1891.

Kolb, K.—"Ein Beitrag zu den Misserfolgen mit Antimeristem (Cancroidin-Schmidt)," *Münch. med. Woch.,* 1911, p. 1076.

Mattei, Cæsar.—"Electro-Homeopathy. The Principles of a New Science, Discovered by Count Mattei of Bologna," 1880.

More Secret Remedies. What they cost and what they contain. Based on Analyses made for the Brit. Med. Assn., Secret Rem., 2d Series, London, 1912.

"Mrs. Van Niekirk's Cancer Cure: The Report of the Select Committee of the Cape House of Assembly," *So. African Med. Rec.,* Aug. 25, 1906, p. 234.

Morris, Sir Henry.—"The Treatment of Inoperable Cancer," Second International Surgical Congress, Brussels, 1908, Vol. II, p. 295.

Myler, J. W. Glenton.—"Some empirical Methods adopted in the Treatment of Inoperable Cancer and their Results," Arch. of Middlesex Hosp., Second Report of the Cancer Research Laboratories, 1904, Vol. II., p. 65.

Myler, J. W. G.—"'Otto Schmidt' Treatment for Cancer: Some empirical methods adopted in the Treatment of Inoperable Cancer and their results," Arch. Middlesex Hosp. (Cancer Res.), 1904, ii, 65.

Paine, Alexander, and Morgan, David J.—"A Paper on the Value of a Serum (Doyen's) in Cases of Malignant Disease," Med. Chir. Trans., Pub. by the Roy. Med. and Chir. Soc. of London, 1906, Vol. LXXXIX, p. 707.

Rowntree, Cecil.—Article on Tumors, in "A System of Treatment," edited by Arthur Latham and T. Crisp English, 1912.

Schmidt, Otto.—"Die Wirkungsweise des Antimeristem bei der Krebsbehandlung," *Zeitschr. für aerztliche Fortbildung*, No. 12, 1911, p. 649.

"Secret Remedies. What they Cost and What they Contain: Based on Analyses for the Brit. Med. Assn.," London, 1909.

Shaw-Mackenzie.—"The Nature and Treatment of Cancer," 1905.

Stead, W. T.—"Can Cancer Be Cured? A Visit to Count Mattei: His Challenge to the Faculty. With Letters from Prof. Huxley, Prof. Tyndall, Sir Morell Mackenzie, Prof. Ray Lankester, and Others," *Review of Reviews*, January, 1891.

Thomas, J. Lynn.—"A note upon a case of cancer of the right breast 'cured' by the Cardigan 'cancer curers.' The Aftermath: A danger-signal to the public," *Brit. Med. Jour.*, Dec. 5, 1908, ii, p. 1677. With special plate.

NON-SURGICAL TREATMENT

(1) Caustics or Escharotics
(2) Physiotherapy
(3) Biotherapy
(4) Miscellaneous Agents

Caustics or Escharotics—Miscellaneous Agents

Blumenthal, A.—"Les résultats éloignés du traitement de la carcinomatose par l'électro-sélénium," *Presse méd. Belge*, Brux., 1913, lxv, 919.

Blumenthal, A.—"De la réaction fébrile consécutive aux injections intra-veineuses de sélénium colloidale," *Poitou méd.*, Pontiers, 1913, xxviii, 238.

Cerny and Trunecek.—"Guérison radicale du cancer épithéliale," *Semaine médicale*, May, 1897, xvii, p. 161.

Delbet, P.—"Tentatives de traitement de cancer par le sélénium," Bull. de l'assoc. franç. pour l'étude du cancer, Paris, 1912, v. 121-125.

Braunstein, A.—"Chemotherapeutische Versuche an Krebskranken mittels Seleniodmethylenblau," *Berl. klin. Woch.*, 1913, No. 24, p. 1102.

Delbet, P.—"Traitement des cancers par le sélénium," Bull. de l'assoc. franç. p. l'étude du cancer, Paris, 1913, xi, 85-90.

Gaylord, Harvey R.—"Ueber die therapeutische Wirkung der Metalle auf Krebs," *Berl. klin. Woch.*, Oct. 21, 1912, 49, p. 2017.

Gelarie, A. J.—"The Influence of Copper upon the Growth of Mouse Carcinoma," *Brit. Med. Jour.*, Aug. 2, 1913, p. 222.

Lewin, Carl.—"Die Wirkung von Schwermetallen auf die bösartigem Tiergeschwülste," *Berl. klin. Woch.*, Mar. 2, 1913, 50, p. 541.

Loeb, L.—"The treatment of human cancer with intravenous injections of colloidal copper," *Interstate Med. Jour.*, St. Louis, 1912, xix, 1015-1022; Further observations, *ibid.*, 1913, xx, 9-16.

Moore, C. H.—"Treatment by Caustics," in "A System of Surgery, theoretical and practical, in treatises by various authors," edited by T. Holmes, 2d ed., Vol. I, General Pathology, pp. 605-607, London, 1870.

Park, Roswell.—"Recent Views Concerning the Treatment of Cancer, Based upon its Nature," *Buffalo Med. Jour.*, April, 1911, LXVI, p. 465.

Pusey, William Allen.—"The Principles and Practice of Dermatology," 1911, pp. 912-13.

Pye-Smith, R. J.—"Arsenic cancer, with description of a case," Proc. Roy. Soc. Med., Lond., 1912-13, vi, Clin. Sect., 229-236.

Spude, H.—"Erfolgreiche Behandlung von Gesichtskrebsen durch einfache Einstichelung von Eisenoxyduloxid," Vorläufige Mitteilung. *Ztschr. f. Krebsf.*, Berl., 1913, xiii, 139-143.

Spude, H.—"Erfolgreiche Behandlung von Gesichtskrebse durch Einstichelung von Eisenoxyduloxyd kombiniert mit Arseninjektionen," *Berl. klin. Woch.*, 1913, l, 1104.

Stelwagon, Henry W.—"Diseases of the Skin," 1914, p. 885.

Vignat, Marcel.—"Contribution à l'étude de la Méthode de Cerny et Trunecek," Thèse de Paris, 1900.

Physiotherapy

Abbe, Robert.—"Radium as a specific in Giant-cell sarcoma," *Med. Rec.*, Jan. 1, 1910, 77, p. 1.

Abel (Berlin).—"Erfahrungen über die Fulguration von Carcinomen nach de Keating-Hart," *Archiv f. klinische Chirurgie*, 1909, xc, 298.

Adams, George.—An Essay on Electricity, Explaining the Principles of that Useful Science; and describing the Instruments Contrived either to illustrate the theory, or render the Practice entertaining, etc., 4th edition, 1792, p. 494.

Aschoff, Krönig, und Gauss.—"Zur Frage der Beeinflussbarkeit tiefliegender Krebse durch strahlende Energie," *Münch. med. Woch.*, 1913, lx, 337; 413, 1 pl.

Bainbridge, W. S.—"The de Keating-Hart Method of Fulguration and Thermoradiotherapy," *Med. Rec.*, July 6 and 20, 1, 1912.

Bainbridge, W. S.—"The use of certain physical agents in the treatment of cancer and allied diseases: (1) electrocoagulation (Doyen); (2) fulguration (de Keating-Hart); (3) thermoradiotherapy (de Keating-Hart), Internat. Clin., Phila., 1913, 23s., Vol. III, 268-285.

Bainbridge, W. S.—"Fulguration and Thermoradiotherapy," *The Jour. of Advanc. Therapeut.*, January, 1913.

Bayet, A.—"Le traitement du cancer par le radium," *Jour. méd. de Bruxelles*, 1913, xviii, 311-319.

Beckton, H., and Russ, S.—"The effect of radium emanations on Altmann's granules," Archives of Middlesex Hosp., 1911, p. 99.

Béclère.—"Le traitement du cancer par le radiothérapie," *Paris méd.*, Feb. 4, 1911, No. 10.

Béclère.—"Cancer et radiothérapie," *Prog. méd.*, Paris, 1907, 3s, xxiii, 1-4.

Bergonié, J.—"Diathermia as an excess ration," *Jour. Adv. Therap.*, New York, 1913.

Bergonié et Réchou.—"La diathermie; applications médicales et chirurgicales," *Arch. d'Electric. méd.*, July 25, 1911, p. 71.

Bevan, A. D.—"The X-ray as a therapeutic agent with especial reference to Carcinoma," *Jour. Am. Med. Assn.*, Chicago, 1904, xlii, 26-30.

Bie, V.—"Remarks on Finsen's Phototherapy," *Brit. Med. Jour.*, 1899, Vol. II, p. 825.

Bie, V.—"Behandlung von Hautepitheliomen mit concentrirten Licht," *Dermat. Ztschr.*, Berl., 1900, vii, 630-41.

Bouchacourt et Chéron.—"De l'association de la radium thérapié à la radio thérapie dans le traitement des fibromes utérins." Bull. de la Soc. d'Obst. et de Gynécol. de Paris (Sess. July 8), 1912, xv, 741-753.

Braunstein, A. (Moscow).—"Wer hat die Radiumemanation in die Therapie eingeführt?" *Deutsch. med. Woch.*, Leipz. u. Berl., 1911, xxxvii, 507 (Korrespondenzen).

Broca.—"Guérison par les rayons X de lésions épithéliomateuses dues aux rayons X eux-mêmes," Abstr. in *Arch. d'électric. méd.*, 1911, 19 (Pt. 2), p. 146 (Congrès de Dijon, July 31-Aug. 5).

Broca, A.—"À propos des accidents des aux rayons X," *Arch. d'électric. méd.*, 1911, 19 (Pt. 2), p. 232.

von Bruns, P.—"Krebsbehandlung mit Röntgenstrahlen," *Therap. der Gegenw.*, Berl., 1904, xlv, 28-33.

Bumm.—"Ueber Erfolge der Röntgen und Mesothoriumbestrahlung beim Uterus Karzinom," *Berl. klin. Woch.*, 1913, pp. 1001 and 1033.

Bumm, E., und Voigt, H.—"Zur Technik der Carcinombestrahlung," *Münch. med. Woch.*, 1913, lx, 1697-1701.

Burgsdorf, V.—"Curative and Noxious Powers of Light," *Kazan Med. Jour.*, 1903, Vol. II, 517-528.

Byrne, John.—"A Digest of Twenty Years' Experience in the Treatment of Uterine Cancer by Galvanocautery," Trans. Am. Gyn. Soc., 1889, Vol. XIV, p. 79-101.

Byrne, John.—"Vaginal Hysterectomy and High Amputation, for partial Extirpation by Galvanocautery in Cancer of Cervix Uteri. An Inquiry into their relative merits," *Brooklyn Med. Jour.*, November, 1892, vi, 729-766.

Byrne, John.—"Rules to be observed in Performing High Amputation and Other Operative Measures for Cancer of the Uterus by Galvanocautery," *Brooklyn Med. Journal*, November, 1892, 6, p. 760.

Byrne, John.—"Electro-Thermal Surgery-Galvanocautery, Internat. System of Electrotherapeutics," 2d ed., p. 169.

Bythell, W. J. S., and Barclay, A. E.—"X-ray Diagnosis and Treatment," London, 1912.

Chéron et Rubens-Duval.—"De la radiumthérapie des cancers végétants du col utérin," Abstr. in *Arch d'électric. méd.*, 1911, 19, Pt. 2, p. 150 (Congrès de Dijon, July 31-Aug. 5).

Clark, William L.—"Oscillatory Desiccation in the Treatment of Accessible Malignant Growths and Minor Surgical Conditions. A new Electrical Effect," *Jour. of Advanced Therapeutics*, 1911, Vol. XXIX, p. 169.

Clunet, J.—"Tumeur developpée sur une radiodermite expérimentale: Recherches Expérimentales sur les Tumeurs Malignes," Paris, 1910, Chap. X, pp. 297-312.

Coley, W. B.—"Late results of X-ray treatment of sarcoma," *Med. News*, N. Y., 1904, lxxxiv, 246-249.

Coley, W. B.—"Later Results of the X-ray Treatment of Sarcoma," *Archives of Physiol. Therapy*, 1908, Vol. III, p. 161.

Coolidge, W. D.—"Physical Review of the American Physical Society," December, 1913.

Cornil et Péraire.—"Épithéliome tubulé du sein traité pendant dix mois par la radiothérapie; aucune modification dans la tumeur," Bull. et mém. Soc. anat. de Paris, 1905, lxxx, 529.

Czerny, Vinzenz.—"Ueber den Gebrauch der Fulguration und der Kreuznach Radiolpräparate bei der Behandlung der Krebse," *Arch. f. klin. Chir.*, 1909, xc, 137.

Czerny, Vinzenz.—"Ueber Therapie des Krebses," *Münch. med. Woch.*, 1911, lviii, pp. 1735-1737; in *Presse méd.*, Jan. 6, 1912, No. 2, p. 23.

Czerny, Vinzenz.—"Ueber die nichtoperative Behandlung der Geschwülste" (Versamml. Deutsch. Naturf. u. Aerzte in Münster), *Ztschr. f. Krebsf.*, 1912-13, Vol. XII, p. 612.

Czerny, Vinzenz, und Caan, Albert.—"Ueber die Behandlung bösartiger Geschwülste mit Mesothorium und Thorium X," *Münch. med. Woch.*, 1912, 59, p. 737.

Danlos, H.—"Sur l'action physiologique et thérapeutique du radium," Bull. d. Sci. pharmacol., Paris, 1904, lx, 65-74.

Delbet, Pierre.—"Behandlung der bösartigen Tumoren mit Radium," *Münch. med. Woch.*, 1909, 56, 1974 (Vereins Berichte).

Dominici, M. H.—"Du traitement des tumeurs malignes par le rayonnement ultrapénétrant du radium," Bull. de l'assoc. franç. pour l'étude du cancer, Dec. 21, 1908, in *Rev. de méd.*, 1909, p. 124.

Dominici, M. H., et de Martel.—"Radiumthérapie du cancer de la langue," *La Presse médicale*, 1910, No. 18, p. 155.

Dominici, H., and Warden, A. A.—"The Technique and Results of Radium-Therapy in Malignant Disease, With Special Plate," *Brit. Med. Jour.*, 1910, Vol. II, p. 516.

Dominici, H., et Chéron, H.—"Le traitement des cancers profonds par le radium," *Arch. d'électricité méd.*, 1911, 19 (Pt. 2), p. 21.

Dupeyrac, M.—"Statistique de quatorze ans de cancers traités par le radium," Abstr. in *Arch. d'électric. méd.*, Aug. 10, 1911, p. 144 (Ass. franç. pour l'avancement des sciences, Congrès de Dijon, July 31-Aug. 5, 1911).

Edling, L.—"Radium Treatment of Malignant Tumors of the Uterus," *Nordisk. Med. Arkiv*, 1911, Vol. XLIV, No. 16, p. 1.

Ehrmann et Lafont.—"Filtration et fortes doses dans le traitement des épithéliomas cutanés," *Arch. d'électric. méd.*, 1912, 20 (Pt. 1), p. 422; (Soc. de rad. méd. de Paris, Sess. Apr. 9, 1912).

Evler.—"Autoserothérapie bei Bauchfelltuberkulose durch Dauerdrainage des Aszites unter die Haut," *Med. Klinik*, 1910, 6, p. 627.

Exner, A.—"Ueber Dauerheilungen von Karzinom nach Radiumbestrahlung," *Münch. med. Woch.*, 1910, 57, p. 2472; also "Sitzungsber. der K. K. Akad. d. Wissensch.," Wien, 1903, Vol. CXII, Abt. iii, p. 285.

Exner, A., und Holzknecht, Guido.—"Die Pathologie der Radiumdermatitis," *Ibid.*, p. 155.

Exner, Alfred.—"Ueber die Behandlung von Oesophagus-Karzinomen mit Radiumstrahlen," *Wien. klin. Woch.*, 1904, 17, p. 96; also "Ueber die Art der Ruckbildung von Karzinommetastasen unter der Einwirkung der Radiumstrahlen," *Ibid.*, p. 181; also *Deutsch. Ztschr. f. Chir.*, 1905, 75, p. 379.

Fehling, H.—"Ueber die Bedeutung der radioaktiven Mittel für die Krebsbehandlung," *Strassb. med. Ztg.*, 1912, x, 241-9.

Finsen, Niels R.—"The Treatment of Lupus vulgaris by Concentrated Chemical Rays": Appendix to Phototherapy, 1901. Published earlier in 1899. See also "Mödd. om de hidtil opnaaede Resultater

af Behandlingen af Hudepitheliomer med. konc. Lys," Dermat. Selskabe Fordhandlinger, 1899-1900.
Finzi, N. S.—"The Radium Treatment of Cancer; Experiences of over 100 cases," *The Lancet*, London, May 20, 1911, p. 1339.
Finzi, N. S.—"Radium Therapeutics," London, 1913.
Fowler, Frank.—"The Technique of X-ray Treatment of Cancer," Brit. Med. Assn., *Brit. Med. Jour.*, Oct. 11, 1913, ii, 912.
Frederick, Carlton C.—"Use of the Cautery in Treatment of Carcinoma of the Cervix," *Jour. Am. Med. Assn.*, January 14, 1911, 56, p. 94.
Gould, Sir Alfred Pearce.—"The use of Gamma Radiation in Surgery (Discussion on Radium and Radiotherapeutics, chiefly in malignant Growths," Brit. Med. Assn.), *Brit. Med. Jour.*, Oct. 11, 1913, p. 908.
Gould, Sir Alfred Pearce.—"An Address on Radium and Cancer, delivered at the Annual Meeting of the West Somerset Branch of the Brit. Med. Assn. at Taunton, Dec. 9, 1913, *Brit. Med. Jour.*, Jan. 3, 1914; Letter in reply to criticism by Mr. John Morley in which Pearce Gould says that "disappearance of growth" and "cure of cancer" are far from being synonymous and cites two cases in which improvement was not maintained.
Gould, Sir Alfred Pearce.—The Purvis Lecture—The Treatment of Inoperable Cancer, Archives of the Roentgen Ray, March, 1913, Vol. XVII, p. 399.
Gould, Sir Alfred Pearce.—"An Address on Radium and Cancer," *Brit. Med. Jour.*, Jan. 3, 1914, p. 1.
Gunsett, A.—"La Question du mésothorium dans le traitement du cancer en Allemagne," *Arch. d'électric. méd.*, 1913, 21, p. 102.
Gunsett, A.—"La Question du Radium dans le traitement du cancer," 85 Cong. Allemand de méd. et d'Hist. naturelle, Vienna, 1913; *Arch. d'électric. méd.*, 1913, 21, p. 436.
Hahn, O.—"Ein neues radioaktives Element, welches Thoriumstrahlen aussendet," *Ztschr. f. phys. Chemie*, Leipzig, 1905, li, 717. Translated (abstract) in *Chem. News*, London, 1905, xcl, 193.
Hyde.—"Influence of light in the production of Cancer," *Am. Jour. Med. Sci.*, 1906, xxxi, n. s. p. 22. (Long bibliography.)
Johnson, Francis Hernaman.—"On the Indication for Radiation, Before, During, and After Operation for Cancer," *Brit. Med. Jour.*, Oct. 11, 1913 (Sect. on Electro-Therapeutics, 81 Ann. Meeting of Brit. Med. Assn.).
Johnson, W. J., and Merrill, W. H.—"The X-rays in the Treatment of Carcinoma," *Phila. Med. Jour.*, 1900, Vol. VI, p. 1089.
Jones, Henry Lewis.—"Medical Electricity," London, 1906, 5th ed.
Kafemann.—"Die nichtoperative Behandlung des Krebses nach den Grundsatzen des Heidelberger Samariterhauses," *Medizin. Klin.*, Berl., 1913, ix, 161-168.
Kassabian, Mihran Krikor.—"Röntgen Rays and Electrotherapeutics; with Chapters on Radium and Phototherapy," Philadelphia and London, 1910, 77 pls.
De Keating-Hart.—"La fulguration et ses résultats d'après une statistique personelle de 247 cas," Paris, Maloine édit., 1909.
De Keating-Hart.—"Présentation de six cancers traités par la fulguration. Étude et conclusions," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, 3, 243.
De Keating-Hart.—"Actions comparées de la fulguration dans le traitement du cancer," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, 3, 327-339.

De Keating-Hart.—"Vingt-cinq cancers traités avec succès par la fulguration; Réponse à M. Pierre Delbet," Bull. de l'assoc. franç. pour l'étude du cancer, 1911, 4, 120. (And Discussion.)

De Keating-Hart.—"Deux traitements physiothérapiques du cancer en stomatologie," Rev. de stomatologie, Par., 1912, xix, 540-554.

De Keating-Hart.—"The rational treatment of cancer," *Practitioner*, Lond., 1913, xci, 669-674.

Klemperer.—"Ein Fall von Carcinome Röntgen," Verein f. inn. Mediz. u. Kinderheilk., Berl., Nov. 20, 1911.

Krönig et Gauss.—"La radiothérapie en gynécologie. Radio ou radium thérapie?" *Arch. d'électric. méd.*, 1913, 21, pt. 2, p. 236.

Lambert, Robert A.—"Demonstration of the Greater Susceptibility to Heat of Sarcoma Cells as Compared with Actively proliferating Connective Tissue Cells," *Jour. Am. Med. Assn.*, Dec. 14, 1912, 59, p. 2147.

Lazarus-Barlow, W. S., and Beckton, H.—"Note on the 'time factor' in calculating 'radium dose,'" Archives of Middlesex Hosp., Lond., 1911, xxx, 77-83.

Lazarus, Paul.—"Handbuch der Radium-Biologie und Therapie," Wiesbaden, 1913.

Lazarus, P.—"Zur Radiotherapie der Carcinome," *Berl. klin. Woch.*, 1913, l, 1304.

Lazarus-Barlow, W. S.—"The Croonian Lectures on Radioactivity and Carcinoma: An Experimental Inquiry," *Brit. Med. Jour.*, June 19 and 26, 1909, pp. 1465, 1536.

Lazarus-Barlow.—"The Cause and Cure of Cancer viewed in the Light of recent Radiological Research," *Brit. Med. Jour.*, May 9, 1914, Vol. I, p. 1001.

Ledoux-Lebard, R.—"Les injections de radium insolubles chez les cancéreux inoperables," *Jour. de Radiologie*, June 30, 1912, p. 205; also Bull. gén. de thérap., 1912, Vol. 164, pp. 477, 478, 479; also abstr. from *Jour. de Radiol.* in *La Presse méd.*, July 27, 1912, p. 640.

Ledoux-Lebard.—"Les injections de sulfate de radium insolubles chez les cancéreux inopérables," *Arch. d'électric. méd.*, Bordeaux, 1913, xxiii, 97-101; also in Bull. de l'assoc. franç. pour l'étude du cancer, 1912, 5, 180.

Levy-Dorn.—"Zur Wirkung der Röntgenstrahlen auf malignen Geschwültse," *Strahlentherapie*, Berl., 1913, iii, 210-215.

Linnert, Gerhard.—"Experimentelle und klinische Untersuchungen über die Wirkung radioaktiver Substanzen insonderheit des Mesothoriumbromid," Halle a/S, 1913.

MacKee, George M.—"Epithelioma Treated with the Massive-Dose Method," *Jour. of Cutaneous Diseases*, 1913, Vol. 31, p. 411.

MacKee, G. M.—"Massive dose X-ray treatment of cutaneous epithelioma," *New York Med. Jour.*, 1913, xcvii, 633-642.

Magnon-Pujo, Gaston.—"Contribution à l'étude de la radiothérapie des tumeurs profondes, technique à employer," *Bull. de Thérapeut.*, Jan. 15, 1911, p. 72.

Marie, Pierre, et Clunet, Jean.—"Action des rayons X sur les tumeurs malignes," *La Presse méd.*, Oct. 22, 1910, No. 85, p. 790.

Marie, Pierre, Clunet, Jean, et Raulot-Lapointe, Gaston.—"Contribution à l'étude du développement des tumeurs malignes sur les ulcères de Röntgen, Bull. de l'assoc. franç. pour l'étude du cancer," 1910, 8, 404-426.

Marie, P., Clunet, J., and Raulot-Lapointe, G.—"Nouveau cas de tumeur maligne provoquée par une radiodermite experimentale chez le rat blanc," Bull. de l'assoc. franç. pour l'étude du cancer, 1912, 5, p. 125.

Massey, G. Betton.—"Ionic Surgery in the Treatment of Cancer," 1910.

Massey, G. Betton.—"Gynecology and Electrochemical Surgery," *Jour. of Advanced Therapeutics,* March, 1911, Vol. XXIX, p. 139.

Ménétrier et Clunet.—Contribution à l'étude de la radiothérapie des cancers épitheliaux," *Arch. de méd. expér.,* Paris, 1908, Vol. XX, 159-188.

Morin.—"Réaction précore après radiothérapie," *Arch. d'électric. méd.,* 1911, 19 (Pt. 2), p. 235.

Morris, Malcolm, and Dore, Ernest.—"Further Remarks on Finsen's Light and X-ray Treatment in Lupus and Rodent Ulcer," *Brit. Med. Jour.,* 1902, i, p. 1324.

Moullin, C. W. Mansell.—"The Treatment of Sarcoma and Carcinoma by Injections of the Mixed Toxins," London, 1898.

Muller, Ch.—"Un nouveau mode de traitement des tumeurs malignes," *Bull. gén. de thérapeut.,* Jan. 30, 1911, p. 157.

Nagelschmidt, F.—"The Thermal Effects Produced by High-frequency currents and the Therapeutical Uses of Diathermic Treatment," Proc. Roy. Soc. of Med., Lond., Oct. 21, 1910.

Nagelschmidt, F.—"Effets thermiques, produits par les courants de haute fréquence sur p'organisme (Rapport presenté au IIIème Cong. Internat. de Physiothérapie, Paris, Mar. 29-Apr. 3, 1910), *Arch. d'électric. méd.,* 1910, 18, p. 161; also Archives of the Roentgen Ray, 1910-11, Vol. XV, p. 58; also, "The Method of Diathermy in Medicine, *Ibid.,* pp. 132-140.

Nagelschmidt, F.—"The Method of Diathermy in Surgery," Arch. Roentg. Ray, Lond., 1910-11, xv, 132-140.

Nagelschmidt, F.—"Ueber Diathermie (Transthermie, Thermopénétration)," *Münch. med. Woch.,* 1909, lvi, 741-744.

Nagelschmidt, F.—Lehrbuch der Diathermie für Aertzte u. Studiérende, Berlin, 1913.

Percy, J. F.—"The Results of the Treatment of Cancer of the Uterus by the Actual Cautery, with a Practical Method of its Application," *Jour. Am. Med. Assn.,* 1913, lviii, 696.

Percy, J. F.—"A Method of Applying Heat both to Inhibit and Destroy Inoperable Carcinoma of the Uterus and Vagina," *Surg. Gyn. and Obst.,* September, 1913, p. 371.

Petersen, O. V.—"Progress of Phototherapy by Finsen's Method," *Vrach,* St. Petersburg, 1901, xxii, 1369.

Pinch, A. E. Hayward.—"A Report of the Work Carried out at the Radium Institute, from Aug. 14, 1911, to Dec. 31, 1912," *Brit. Med. Jour.,* Jan. 25, 1913.

Pinkuss, A.—"Zur Mesothoriumtherapie bei Krebskranken," *Berl. klin. Woch.,* 1912, No. 20, p. 935.

Pinkuss, A.—"Die Behandlung des Krebses mit Mesothorium und ihre Kombination mit anderen Verfahren," *Deutsch. med. Woch.,* 1913, xxxix, 1720-1723; "Des résultats obtenus dans le traitement du cancer par l'emploi thérapeutique du mésothorium," *Arch. d'électric. méd.,* Bordeaux, 1913, xxiii, 113-116.

Pinkuss, A.—"Ueber die Erfogle der Mesothoriumbestrahlung der Carcinom," *Berl. klin. Woch.,* 1913, l, 1105-1107.

Pinkuss, A.—"Des résultats obtenus dans le traitement du cancer par l'emploi thérapeutique du mésothorium," *Arch. d'électric. méd.*, 1913, 23, p. 113.

Porter, C. A., and White, C. J.—"Multiple Carcinomata Following Chronic X-ray Dermatitis," *Annals of Surgery*, 1907, Vol. XLVI, p. 649.

Rivière, J. A.—"Action of High Frequency Currents and of the Effluves of Oudin's Resonator on Certain Malignant Tumors and on Tuberculosis," First Internat. Congress of Med. Electrology and Radiology, Paris, July 27-Aug. 1, 1900.

Rivière.—"Les agents physiques appliques à la guérison du cancer," *Gaz. méd. Belge*, Liège, 1903-4, xvi, 137.

Rivière, J. A.—"Alto-Frequent Cytolysis of Cancer," *Jour. of Advanced Therapeutics*, 1909, pp. 337, 380, 434.

Rivière, J. A.—"Esquisses cliniques de Physicothérapie-Traitement rationnel des maladies chroniques," Paris, 1910.

Rivière, J. A.—"La physicothérapie du Cancer," *Ann. d. méd. phys.*, Anvers, 1913, xi, 335-353.

Rowntree, Cecil W.—"Contribution to the Study of X-ray Carcinoma and the conditions which precede its onset," Archives of Middlesex Hospital, July, 1908, Vol. XIII, p. 182; and Vol. XV, p. 192.

Sack.—"Ulcus rodens and Finsen light," *Münch. med. Woch.*, 1902, p. 1142.

Sarazin, C.—"L'ionization et l'introduction électrolytique des médicaments," *Arch. méd. d'Angers*, 1913, xvii, 225, 257, 312.

Schmidt, H. E.—"Experimentelle Untersuchungen über die wirkung kleinerer und grosserer Röntgenstrahlenmengen auf junge Zellen," *Berl. klin. Woch.*, 1910, xlvii, p. 972.

Schultz, F.—"Die Röntgentherapie in der Dermatologie," 1910, Transl. into English by James Burnet, New York, 1912.

Schumann, E.—"Ueber die Entstehung bösartiger Neubildungen auf der Röntgenbestrahlten Haut," *Arch. f. klin. Chir.*, 1907, Vol. LXXXIV, p. 855.

Seelye, Hiram H.—"Cutaneous Epitheliomata Cured by Sunlight," *New York Med. Jour.*, Feb. 7, 1914, p. 279.

Ségond.—"Régression sous l'influence du radium d'un sarcoma globocellulaire pur à évolution rapide ayant débuté au niveau du maxillaire inférieure," Bull. et Mém. Soc. de Chir. de Paris, 1911, n. s. xxxvii, 435-445.

Smith and Wilson.—"Treatment of cancer by radium and its derivatives," Guy's Hosp. Repts., Vol. LXV, p. 131.

Solis, Jeanne.—"Ionization in the treatment of Superficial Epithelioma," *Jour. Mich. Med. Soc.*, Battle Creek, 1913, xii, 99-102.

Spude, H.—"Die ersten Versuche mit einer neuen Kombinationsbehandlung des Krebses (Elektromagnetische Reiz-Arsenbehandlung)," *Ztschr. f. Krebsf.*, 1912-13, Vol. XII, p. 255.

von Tappeiner and Jesionek.—"Therapeutische Versuche mit fluoreszierenden Stoffen," *Münch. med. Woch.*, Nov. 24, 1903, p. 2042; abstr. in *Sem. méd.* 1903, p. 422; and in *Rev. Internat. d'electrothérapie*, Jan., 1904, No. 13, p. 212.

Thayer, O. V.—"Concentrated rays of the sun (solar cautery) as a remedial agent," *Pacific Med. Jour.*, San Francisco, 1893, xxxvi, 412-419; also *South. Pract.*, Nashville, 1893, xv, 360-367; also "The Treatment of Cancer, Lupus, and other Malignant Growths, with Concentrated Sun's Rays.—Solar Cautery," *Pacific Med. Jour.*, 1902, xlv, 193.

Theilhaber, A.—"Zur Frage von der operationslösen Behandlung des Carcinoms," *Berl. klin. Woch.*, 1913, 1, 348.

Tousey, Sinclair.—"Medical Electricity and Röntgen Rays," 1910.

Tuffier, T.—"Les rayons X et la thérapeutique du cancer," *Presse méd.*, Paris, 1904, i, 73-75; also "Radiothérapie dans le cancer," soc. de chir. de Par., 1903, n. s. xxxix, 1078-1082.

Tuffier, T.—"Epithéliome de la face traité par la radiothérapie," Bull. et mém. soc. de chir. de Paris, 1903, n. s. xxix, 1172.

Warden, A. A.—"Radium and Inoperable Cancer," *Brit. Med. Jour.*, Oct. 25, 1913, ii, p. 1067.

Warden, A. A.—"Inoperable cancer and radium; some experiences," *Practitioner*, Lond., 1913, xci, 19-32.

Werner, R., and Caan, Albert.—"Ueber die Wirkung von Röntgen strahlen auf Geschwültse," *Münch. med. Woch.*, 1910, LVII, 1384.

Werner, R., und Caan, A.—"Ueber die Vorlagerung intra-abdomineller Organe zu Röntgenbestrahlung," *Münch. med. Woch.*, Mar. 14, 1911, 58, p. 553.

Wickham, L.—"The therapeutic application of radium to cancer and other tumors," *Lancet*, Lond., 1909, i, 1546-1548.

Wickham and Degrais.—"Radium Therapy," Trans. by S. E. Dore, with an introductory note by Sir Malcolm Morris, Lond., 1910.

Wickham and Degrais.—"Radium and Cancer," London, 1913; Transl. by A. and A. G. Bateman.

Wickham, Louis, and Degrais, Paul.—Radium as employed in the treatment of cancer, angiomata, keloids, local tuberculosis, and other affections, Transl. by A. & A. G. Bateman, Lond., 1913.

Widmer, C.—"Heilung eines Karzinoms durch Sonnenlicht nebst einigen Beiträgen zur unmittelbaren Lihtherapie," *Münch. med. Woch.*, 1907, liv, 619.

Williams, Ennion G.—X-ray Treatment of Malignant Growths, Trans. Coll. Phys., Phila., 1905, 3s, xxvii, 23-33.

Williams, Ennion G.—"The regulation and measurement of the therapeutic dose of the Roentgen Ray," *Arch. physiol. Therapy,* Boston, 1906, iii, 70-74.

Williams, Ennion G.—"The Post-operative Treatment of Malignant Disease," *Am. Jour. Med. Sci.*, Phila. and New York, 1909, cxxxvii, 45-49.

Zimmer, A.—"Enterale Ionentherapie," *Med. Klin.*, Berl., 1912, viii, 1025-1027; also "Zur Therapie enterogene Erkränkungen," *Wien. med. Woch.*, 1912, lxii, 1350-1355.

Biotherapy

Babcock, W. Wayne.—"Fetal Products in the Treatment of Carcinoma (Fichera's Method)," "International Clinics," Vol. II, 23 Ser., p. 81.

Bergell, P., and Lewin, C.—"Ueber Pathogenese und über den spezifischen Abbau der Krebsgeschwülste," *Ztschr. f. klin. Med.*, 1907, Vol. LXIV, No. X, p. 185.

Berger, Paul.—Discussion on Wlaeff's serum, Bull. et Mem. Soc. de Chir. de Paris, 1901, xxvii, p. 174.

Blumenthal, Ferdinand.—"Rückbildung bösartigen Geschwülste durch die Behandlung mit den eigenen Tumorextract (Autovaccine)," *Ztschr. f. Krebsf.*, 1912-13, Vol. II, p. 427.

Bruns, P.—"Zur Krebsbehandlung mit Erysipelseum," *Deutsch. med. Woch.*, 1895, xxi, pp. 313, 428; *Semaine méd.*, 1895, 236.

Busch, W.—"Einfluss der Erysipels auf organisirte Neubildungen," *Berl. klin. Woch.*, 1866 (Sess. of Mar. 14), p. 245.

Carnot.—"Opotherapie," Paris, 1911.

Coca, Arthur F.—"Vaccination in Human Cancer in the Light of the Experimental Data upon Normal Tissue and Tumor Immunity," *Ztschr. f. Krebsf. u. exp. Therap.*, 1912, Vol. 13, p. 524.

Coca.—(Review of "Vaccination"), "Vaccination in Human Cancer in the light of the experimental data upon normal tissue and tumor immunity," *Ztschr. f. Immunitätsf.*, Orig. 1912, xiii, 524.

Coca, Arthur F., Dorrance, G. M., and Lebredo, M. G.—"Vaccination" in "Cancer," *Ztschr. f. Immunitätsf. u. exper. Therap.*, Jena, 1912, xiii, 545-583; *Mulford Digest*, Phila., 1912, l, 96-103.

Coley, W. B.—"Contribution to the Knowledge of Sarcoma," *Annals of Surg.*, 1891, xiv, p. 199; also *Am. Jour. Med. Sci.*, 1893, Vol. CV, n. s., p. 487.

Coley, W. B.—"Late results of Treatment of Inoperable Sarcoma by the mixed toxins of Erysipelas and Bacillus prodigiosus," *Am. Jour. of the Med. Sci.*, March, 1906, p. 375.

Coley, W. B.—"The value of the mixed toxins of erysipelas and Bacillus prodigiosus in inoperable sarcoma, based upon a study of cases treated during the past sixteen years," *Detroit Med. Jour.*, 1909, xi, 197-205.

Coley, W. B.—"The treatment of inoperable sarcoma by bacterial toxins (the mixed toxins of erysipelas and the Bacillus prodigiosus)," Proc. Roy. Soc. Med., Lond., 1909-10, iii, Surg. Sect., 1-48.

Coley, W. B.—"Round-celled periosteal sarcoma involving two-thirds of shaft of the femur, with extensive metastases in the pectoral and iliolumbar regions; recovery under treatment with the mixed toxins of erysipelas and Bacillus prodigiosus; no recurrence after 9½ years," *Ann. Surg.*, Phila., 1912, lvi, 787.

Coley, W. B.—"Contribution to the Study of Sarcoma of the Femur. Apparent cure by the mixed toxins of erysipelas and Bacillus prodigiosus; well 10½ years when a malignant tumor (sarcoma and epithelioma) developed in the thigh at the site of an old X-ray dermatitis," *Ann. Surg.*, Phila., 1913, lviii, p. 97.

Coley, W. B.—"Sarcoma of the humerus," *Am. Surg.*, Phila., 1911, liii, 286-288; "A round-celled sarcoma of the femur involving two-thirds of the shaft with extensive pectoral and abdominal metastases, well 8½ years after treatment," *Ibid.*, 288-290; "Large inoperable recurrent intra-abdominal sarcoma following removal of a round-celled sarcoma of the testis a year before; disappearance under mixed toxins of erysipelas and Bacillus prodigiosus," *Ibid.*, 299.

Coley, W. B.—"A Report of recent cases of inoperable sarcoma successfully treated with mixed toxins of erysipelas and Bacillus prodigiosus," *Surg. Gynec. and Obst.*, Chicago, 1911, xiii, 174-190.

Coley, W. B.—"Inoperable sarcoma of the scapula in an infant two months old successfully treated with the mixed toxins of erysipelas and Bacillus prodigiosus," *Am. Surg.*, Phila., 1911, liii, 844.

Coley, W. B.—"A plea for more conservative treatment of sarcoma of the long bones," *Jour. Am. Med. Assn.*, Chicago, 1910, liv, 333-343.

Coley, W. B.—"The treatment of inoperable sarcoma with bacterial toxins (The mixed toxins of erysipelas and Bacillus prodigiosus)," Trans. N. Hamp. Med. Soc., 1910.

Czerny.—"Ueber Heilversuche bei malignen Geschwülsten mit Erysipeltoxinen," *Münch. med. Woch.*, 1895, No. 36; also cases in *Ztschr. f. Krebsf.*, 1907, Vol. V, on p. 29.

Diesing.—"Die Wirkung von Schildrüsen Extract auf Magendarmkrebse," *Med. Klinik*, 1911, vii, p. 458.

Emmerich, R., und Scholl, H.—"Klinische Erfahrungen über die Heilung des Krebses durch Krebsserum (Erysipelserum)," *Deutsch. med. Woch.*, 1905, xxi, pp. 265-268.

Eve, Sir Frederic.—"Remarks on the Treatment of Sarcoma of the Long Bones," *The Lancet*, Nov. 16, 1912, p. 1355.

Ewing, James.—"The Treatment of Cancer on Biological Principles," *New York Med. Jour.*, Oct. 19, 1912, p. 773.

Falk, E.—"Injektion von Plazentablut bei Carcinom," *Berl. klin. Woch.*, 1908, Vol. XLV, p. 1394.

Fehleisen.—"Die Aetiologie des Erysipels," Berlin, 1883. (Transl. by Laslie Ogilvie, in "Microparasites in Disease," edited by Watson Cheyne, p. 272.)

"Fetal products in the treatment of carcinoma (Fichera's method)," Internat. Clin., Phila., 1913, 23s., Vol. II, 81-89.

Fichera, G.—"Treatment of Cancer with Autolysates of Human fetuses," *Il Policlinico*, July 3, 1910; abstr. in *Jour. Am. Med. Assn.*, Aug. 6, 1910, p. 545.

Fichera, G.—"Gli autolizzati di tessuti nella terapia dei tumori," *Il Policlinico*, Feb. 12, 1911, p. 197.

Fichera, G.—"Tumori," Turin, 1911; abstr. in *Bull. de l'Inst. Pasteur*, 1911, xi, 272.

Fichera, G.—"The action of the Products of Homogeneous Fetal Autolysis on Malignant Tumors in Man"; transl. from the Italian by Alex. R. Coldstream, *Lancet*, Lond., Oct. 28, 1911, p. 1194.

Fichera, G.—Contributi alla III conferenza internaz. per lo studio del cancro, Tumori, Roma, 1913-14, iii, 161-180.

Foulerton, A. G. R.—"Treatment of Carcinoma with injections of thymus and thyroid gland," Archives of Middlesex Hosp. (Cancer Res.), 1904, ii, p. 143.

Gwyer, Frederick.—"Thymus Gland Treatment of Cancer," *Annals of Surg.*, July, 1907, p. 86; *New York Med. Jour.*, Feb. 19, p. 373.

Hodenpyl, Eugene.—"Treatment of carcinoma with the body fluids of a recovered case. A Preliminary Report," *Med. Rec.*, Feb. 26, 1910, 77, p. 359.

von Jaksch, R.—"Ueber die Behandlung maligner Tumoren mit dem Erysipelserum von Emmerich-Scholl," *Mittheil a. d. Grenzg. d. Med. u. Chir.*, Jena, 1896, i, 318-327.

Lewin, C.—"Die Behandlung von Krebskranke mit Vaccination," *Therap. d. Gegenw.*, June, 1913.

Lewin, C.—"Die Behandlung von Krebskranken mit Vaccination," *Therap. der Gegenw.*, Berl., 1913, liv, 253-257.

von Leyden, E., und Bergell, P.—"Ueber Pathogenese und über den spezifischen Abbau der Krebsgeschwülste," *Deutsch. med. Woch.*, 1907, 33, p. 913.

Lucas-Championnière.—Discussion on Wlaeff's Serum, Bull. et mém. soc. de chir. de Paris, 1901, xxii, p. 174.

Moullin, Mansell.—"The Treatment of Sarcoma and Carcinoma by Injections of Mixed Toxins," London, 1896.

Moullin, C. Mansell.—"The Treatment of Sarcomata by the Injection of Mixed Toxins (Coley's Fluid)": A letter in the *Brit. Med. Jour.*, 1898, ii, p. 451.

Petersen, W.—"Ueber die Grundlage und die Erfolge der Bakterientherapie bösartiger Geschwültse," *Beitr. z. klin. Chir.*, Vol. XVII, No. 10, p. 379.

Pinkuss, A.—"Zur Vaccinationstherapie des Krebses," *Berl. klin. Woch.*, 1913, l, 1941.

Pinkuss and Kloninger.—"Zur Vaccinationstherapie des Krebses," *Berl. klin. Woch.*, Oct. 20, 1913, LX, p. 1941.

Risley, Edward H.—"The Giman-Coca Vaccine Emulsion Treatment of Cancer," *Boston Med. and Surg. Jour.*, Nov. 23, 1911, p. 784.

Roger, S. H.—"Action des produits solubles du stréptocoque de l'érysipèle," Compt. rendus Soc. de Biol., Paris, 1891, 9s., iii, 538-542.

Sanfelice, Francesco.—"Tossine ed antitossine dei blastomiceti patogeni in rapporto alla etiologia ed alla cura dei tumori maligni," *Annali l'Igiene sperimentàle*, 1908, n.s. xviii, p. 521, No. IV, p. 503.

Senn, N.—"The Treatment of Malignant Tumors by the Toxins of the Streptococcus of Erysipelas," *Jour. Am. Med. Assn.*, 1895, xxv, 129-131.

Stimson, L. A., Gerster, A. G., Curtis, B. T.—"Results of Injections of Erysipelas Toxins upon Malignant Growths," *Annals of Surgery*, 1896, xliv, p. 53; also Trans. N. Y. Surg. Soc., 1896. (Report of Committee appointed by the N. Y. Surgical Society.)

Tracy, Martha.—"A Study of the Toxins of Bacillus prodigiosus," *Jour. of Am. Med. Res.*, Boston, 1907, n. s., Vol. XI, 307.

Vaughan, J. W.—"The use of cancer residue," *Jour. Mich. Med. Soc.*, Detroit, 1910, ix, 593-603.

Vaughan, J. W.—"Blood-changes caused by the Hypodermic administration of the Cancer Proteid," *Jour. Am. Med. Assn.*, Nov. 16, 1912, lix, 1764-69.

Vaughan, J. W.—"The Comparative Value of Different Methods of Cancer Treatment," *New York Med. Jour.*, Oct. 15, 1910, p. 759; also *Jour. Am. Med. Assn*, Nov. 16, 1912.

Vaughan, Victor C., Jr.—"The Production of Active Immunity with the Split Products of the Colon Bacillus," *Jour. Med. Res.*, Boston, 1905-6, 9, n. s., p. 67.

Vaughan, Victor C.—"The intracellular toxins of some of the pathogenic bacteria," *Jour. Am. Med. Assn.*, 1903, xi, p. 307.

Vaughan, Victor C. and J. W.—"Protein Split Products in Relation to Immunity and Disease," 1913, xii, 17-476.

Vidal, E.—Discussion ("La résistance des cellules cancéreuses"), etc., Assoc. franç. de chir. 21me Congrès de Chir., Paris, 1908, p. 939; also "Sérothérapies des tumeurs malignes."—A. Études des facteurs qui modifient chez l'animal les pouvoirs d'immunité active et le pouvoir de son sérum, IIme Conférence internat. pour l'étude du Cancer," 1910, p. 315.

Vidal, E.—"A résumé of Serum therapy": Travaux de la deuxième Conférence internat. pour l'étude du Cancer, Paris, 1911, 293.

Volkmann, R.—"Erysipelas," in "Handbuch der allgemeinen und speciellen Chirurgie mit Einschluss der topographischen Anatomie, Operations und Verbandlehre." Edited by Dr. von Pitha and Dr. Billroth, 1865.

Weinberg et Mello, Ugo.—"Quelques recherches sur le sérum des can-

céreux," Bull. de l'Assoc. franç. pour l'étude du cancer, 1910, iii, 42.
Werner (Heidelberg).—"Traitement et diagnostique de la Soc. allemande de chir.," Berl., Apr. 18-22, 1911, im *Presse méd.*, Par., May 10, 1911, No. 37, p. 381.
Wlaeff, G.—"Sérum anticellulaire," Compt. rend. Soc. de Biol. de Paris, 1900, lii, 611-613.
Woods, R. H.—"Carcinoma of the Larynx. Extirpation of primary and secondary growths; glandular recurrence; treatment with thyroid extract; disappearance of growths," *Brit. Med. Jour.*, July 1, 1911, ii, p. 5.
Wyeth, John A.—"The Value of Inoculations with Septic or Toxic Agents in the Treatment of Malignant Neoplasms," New York Polyclinic, July 15, 1894, Vol. IV, No. 1; also *Jour. Am. Med. Assn.*, 1894, xxii, p. 985.
Zartsin, F. O.—"Treatment of cancer by the cancroid of Adamkiewicz," *Vrach. Gaz.*, St. Petersb., 1903, x, therap. pt., 99-102.

Surgical Treatment

Abbe, T.—"Can we improve the results of our operations for cancer?" *Surg. Gynec. and Obst.*, Chicago, 1912, xvi, 185-189.
Astley, Cooper.—"A case of Aneurysm of the Carotid Artery, etc.," Vol. I, 1808 (Operation 1805).
Auvray.—"Sarcome fusocellulaire à myéloplexes de la dure-mère, etc.; hémostase préventive par la méthode Dawbarn-Anschütz," Bull. et mém. soc. de chir. de Paris, 1910, n.s. xxxvi, 1269-1293.
Bainbridge, W. S.—"Metastases following incision of a sarcoma," *New York Polyclin. Jour.*, January, 1908.
Bainbridge, W. S.—"Malignant and Non-malignant Growths," *Am. Jour. of Surg.*, Aug., 1906.
Bainbridge, W. S.—"A clinical lecture of Malignant and Non-malignant Growths," *Atlanta Jour. Rec. of Med.*, June, 1905.
Bainbridge, W. S.—"A Case of Extensive Carcinoma of the Tongue and Neck, Presenting Points of Special Interest," *American Medicine*, Mar., 1905, Vol. IX, No. 12, pp. 477-478.
Bainbridge, W. S.—Malignant and Non-malignant Growths, *Am. Jour. Surg.*, August, 1906.
Bainbridge, W. S.—Some phases of the Surgical Treatment of Cancer —A Clinical Lecture, *Am. Jour. of Surg.*, Nov., 1907.
Bainbridge, W. S.—"Oxygen in Medicine and Surgery—A Contribution, with Report of Cases," *N. Y. State Jour. of Medicine*, June, 1908.
Bainbridge, W. S.—"The Intra-Abdominal Administration of Oxygen," *Annals of Surgery*, March, 1909.
Bainbridge, W. S.—"Arterial ligation, with Lymphatic Block, in the Treatment of advanced Cancer of the Pelvic Organs—a report of fifty-six cases," *Am. Jour. Obst.*, 1913, v, 6, 68.
Bainbridge, W. S.—"Plastic Surgery and Palliative Repair in the Treatment of Malignant Disease." Tenth Annual Clinical Lecture on Cancer, New York Skin and Cancer Hospital, April 26, 1914.
v. Bergmann, E.—"Die chirurgische Behandlung der Hirngeschwülste," Leipzig, 1899; also in Klin. Vorträge, von Volkmann, No. 200 (Chir. No. 57).

Bier, August.—"Unterbindung der Arteriæ iliacæ internæ gegen Prostatahypertrophie," *Wien. klin. Woch.*, Aug. 10, 1893, Vol. VI, p. 583.

Billroth, C. A.—"Die Eintheilung-diagnostik der Geschwülste von chirurgisch-klinischem Standpunkt," *Deutsch Klin.*, 1859, Nos. 40-43.

Billroth, C. A. T.—"Die Krankheiten der Brustdrusen," 1880, Vol. XLI.

Broca.—"Ligature appliquée sur une artère en voie d'ossification," Bull. soc. d. chir. d. Par., 1862, 2 s. ii. 405-407; Sur le choix du bien constricteur dans les ligatures d'artères," Bull. Soc. Imp. de Chir. de Paris, 1865, 2 s. w, 106-114; also *Gaz. d. Hôp.*, Par., 1864, xxxvii, 154.

Broca, P. P.—"Traité des Tumeurs," 2 Vols., Paris, 1886-9.

Bryant, J. D.—"Three cases of ligature of the external carotid artery, in two of which the vessels were tied simultaneously; with remarks on the history of the operation," *Ann. Surg.*, 1887, vi, 115-126.

Cameron, S. J. M.—"The vascular system and the fibromyomata," *Glasgow Med. Jour.*, 1908, lxx, 177-188.

Cantier, P.—"Des ligatures artérielles dans les cancers inopérables de l'utérus," Thèses de Montpellier, 1907.

Cheatle, G. Lenthal.—"The Spread of Cancer of the Tongue, and its Influence on Treatment," *The Practitioner*, Lond., Nov., 1905, n. s. xxii, p. 623; also Remarks in *Brit. Med. Jour.*, 1909, i, 249.

Cheatle, G. Lenthal.—"The Spread of Cancer in the Lower Part of the Large Intestine," *Brit. Med. Jour.*, Feb. 7, 1914, Vol. I, p. 303 (with Special Plate.)

Cheyne, William Watson.—"What can surgery do to relieve sufferers from cancer in various parts of the body?" *The Practitioner*, 1899, Vol. IX, n. s., p. 463.

Clarke, W. Bruce.—"Cases of Persistent Edema Treated by Lymphangioplasty," St. Bartholomew's Hosp. Reports, 1909, xlv.

Crile, G. W.—"On some of the factors that influence the prognosis in operations for cancer," *So. Med. Jour.*, Nashville, 1911, iv, 200-204.

Cripps, Harrison.—"Cancer of the Rectum, especially considered with regard to its Surgical Treatment," London, 1890, 3d ed. (Jacksonian Prize Essay).

Dalrymple, William.—"A case of Aneurism by Anastomosis in the left orbit cured by tying the common trunk of the left carotid artery; operated Apr. 7, 1813" (Communicated by Astley Cooper, Esq.); Read May 23, 1815, Medico-Clin. Trans., 1815, Vol. VI, p. 111.

Dawbarn, Robert H. M.—"The Starvation Operation for Malignancy in the external carotid area—Its failures and successes," *Jour. Am. Med. Assn.*, Sept. 17, 1904, 43, p. 792.

Dawbarn, Robert H. M.—"The Treatment of Malignant Growths by Excision of the external carotids." Samuel Gross Prize Essay, 1903.

Demarquay.—"Ligature des deux artères linguales," *Union méd.*, Paris, 1866, 2 s., xxxii, 508; "Mémoire sur la ligature de l'artère linguale," *Arch. gén. de méd.*, Par., 1868, i, 129-143, transl. in *Allg. wien. med. Zeitung*, 1869, xiv, 147, 157; "Ligature de l'artère linguale," *Gaz. d. Hôp.*, Par., 1873, xlvi, 489; "Note on Ligature of the Lingual Artery in Cases of Cancroid Disease of the Tongue, With Cases," *Brit. Med. Jour.*, 1875, i, 341.

Depage, A.—"Traitement du Cancer du Sein," II Congrès de la Soc. Internat. d. Chir., Brux., 1908, Vol. II, p. 255 (Reports).

Eve, Sir Frederic.—"A Lecture on Melanoma," *The Practitioner,* February, 1903.

Eve, P. F.—"Ligature of Primitive Carotid," *South. Med. and Surg. Jour.,* 1850, n.s., vi, 260-261.

Eve, P. F.—"Fibrous Tumor Attached to Superior Maxillary Bone, with Polypus of the Nose; Ligature to Both Primitive Carotids—Removal of Tumor—Recovery of Patient," *South. Med. and Surg. Jour.,* 1848, n.s., iv, 705.

Ewing, A.—"Case of Extirpation of Tumor, with Ligature of Common Carotid," *Edin. Med. Jour.,* 1832, xxxviii, 18-23.

Franke, F.—"Ueber Versuche mit Dauerdrainage bei Ascites," *Archiv f. klin. Chir.,* 1912, Vol. XCVIII, p. 1059.

Guyon, J. C. Felix.—"Éléments de chirurgie clinique, comprenant le diagnostique chirurgical, les opérations en général, les Méthodes opératoires, le traitement des blessés et des opérés, xxxviii, Paris, 1873. (See p. 245—Ligation of Arteries.)

Halsted, William Stewart.—"Developments in the Skin Grafting Operation for Cancer of the Breast," *Jour. Am. Med. Assn.,* 1913, Vol. LX, Jan.-Mar.

Halsted, W. S.—"The Results of Radical Operation for the Cure of Carcinoma of the Breast," *Ann. Surg.,* Phila., 1907, xlvi, pp. 1-19.

Halsted, W. S.—"The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894," Johns Hopkins Hosp. Repts., Balt., 1894-5, iv, 1-54, 6 pls.; also *Ann. Surg.,* Phila., 1894, xx, 497-555, 4 pls.

Handley, W. Sampson.—"Epigastric Invasion of the Abdomen in Breast Cancer." This Essay was awarded in 1904 the triennial Astley Cooper prize of £500.

Handley, W. Sampson.—"Microscopical Study of the Parietal Dissemination of Mammary Carcinoma," Archives of Middlesex Hosp., Vol. v, Fourth Report Cancer Res. Laboratories, 1905, p. 191.

Handley, W. Sampson.—"On Lymphatic Permeation as a Factor in the Dissemination of Melanotic Sarcoma, with a Note on the Operative Treatment," Archives of Middlesex Hosp., Vol. VII, Fifth Report Cancer Res. Laboratories, 1906, p. 52.

Handley, W. Sampson.—"On Lymphatic Permeation as a Factor in the Dissemination of Melanotic Sarcoma, with a Note on Operative Treatment," Archives of Middlesex Hosp., 1908, vii, p. 52.

Handley, W. Sampson.—"A New Method for the Relief of the Brawny Arm of Breast Cancer and for Similar Conditions of Lymphatic Œdema," *The Lancet,* Lond., Mar. 14, 1908, p. 783; also, Arch. Middlesex Hosp., Vol. 12, p. 28.

Handley, W. Sampson.—"A New Method for the Relief of the Brawny Arm of Breast Cancer and for Similar Conditions of Lymphatic Œdema" (a preliminary note), *The Lancet,* Lond., Mar. 14, 1908, p. 783. See also: "Hunterian Lectures on the Surgery of the Lymphatic System," *Brit. Med. Jour.,* 1910, i, 683, abstr. *Lancet,* 1910, i, 977, 1052; "Elephantiasis Treated by Lymphangioplasty," Proc. Roy. Soc. Med., London, 1908-9, ii, Clin. Sect., 123.

Handley, W. Sampson.—"The Fringes of the Cancer Problem," *Med. Press and Circular,* Dec. 21, 1910, p. 645.

Handley, W. Sampson.—"Recent Advances in the Surgical Treatment of Some Forms of Cancer," *The Universal Med. Rec.,* 1912, v, p. 385-406.

Hartmann, H., et Fredet, P.—"Résultats éloignés de ligatures atrophiantes faites dans deux cas de cancer inopérable de l'utérus," Bull. et Mém. Soc. de Chir. de Paris, 1898, n.s., xxiv, 130-133; also, *Ann. de Gyn. et d'Obst.*, Par., 1898, xlix, 110-129.

Heidenhain, D. L.—"Ueber die Ursache der lokaler Krebsrecidiv nach Amputation Mammæ," *Langenbeck's Archiv*, 1889, 39, 97-166.

Hofmeier.—"De la myotomie abdominale," *Ann. de Gyn. et d'Obst.*, Par., 1898, xlix, 97-110.

Jonnesco, Thomas.—"Traitement chirurgical des kystes hydatiques du Foie," XIII Cong. Int. de Méd., Paris, 1900, Vol. x, p. 227 (Chir. gén.).

Keen, W.—"A Case of Ligature of the Abdominal Aorta Just Below the Diaphragm," etc., XIII Cong. Int. de Méd., Paris, 1900, Vol. X, p. 485.

Kennedy, J. W.—"The Unnecessary Removal of the Pectoral Muscles for Malignancy of the Breast," *Med. Council*, Phila., 1912, xvii, 283.

Koenig, F.—"Lehrbuch der speziellen Chirurgie für Aerzte und Studierende," Berlin, 1875; also, 1889 and 1893-4, 3 vols.

Lannelongue, O. M.—"Leçons de clinique chirurgicale," Paris, 1905.

Levesque, Georges.—"Contribution à l'études des inoculations opératoires du cancer," Par., 1903.

Lockwood, C. B.—"The Objections to the Incomplete Operation for Cancer of the Breast," *Brit. Med. Jour.*, May 23, 1914, p. 1105.

Macewen, J. A. C.—"Carcinoma Uteri: A Clinical Lecture," *Clin. Jour.*, Lond., 1913, xlii, 506-512.

Madelung, O. W.—"Exstirpation eines vom Mesenterium ausgehender Lipoma œdematosum myxomatodes mit partieller Resection des Dünndarmes, Heilung," *Berl. klin. Woch.*, 1881, xviii, pp. 75-78.

Maisonneuve, J. G. Thomas.—"Mémoire sur la ligature extemporanée," Paris, Labe., 1860; also, "Clinique chirurgicale," 2 vols., 1863-4; also, "Des Tumeurs de la Langue," Paris, 1848; also, "Leçons cliniques sur les affections cancéreuses"; recueillies et publiées par M. le Dr. Alexis Favot, 2 Pts., 1852-4; Pt. 1 repr. from *Gaz. des Hôp.*, Par., 1852, xxv; Pt. 2 from *Monit. des Hôp de Par.*, 1853, i, 1854, ii.

Mauclaire.—"Ligatures atrophiantes," *Ann. des mal. des organes génito-urinaires*, 1900, p. 365.

Mauclaire.—"Résultats éloignés du traitement de la tuberculosé épididymo-testiculaire par les ligatures ou les sections des éléments du cordon spermatique ou la funiculotripsie," XIII Cong. int. de méd., Par., 1900, Vol. X, p. 399 (Chir. gén.).

Maunoir, J. P.—"Mémoires physiologiques et pratiques sur l'aneurisme et la ligature des artères," Geneva, 1802.

Mayo, Wm. J.—"Radical Operation for Cancer of the Pyloric End of the Stomach—Review of 266 Partial Gastrectomies," *Jour. Am. Med. Assn.*, May 14, 1910, Vol. LIV, No. 20, p. 1609.

Miles, W. Ernest.—"The Treatment of Carcinoma of the Rectum and Pelvic Colon," *Glasgow Med. Jour.*, February, 1912, Vol. LXXVII, n.s., p. 81; also, *Brit. Med. Jour.*, Oct. 1, 1910.

Mirault, G.—"Mémoire sur la ligature de la langue et sur celle de l'artère linguale en particulier; précédé d'une observation de cancer de la langue guéri par la ligature de cet organe," *Mém. Acad. de Méd.*, 1833-4, Paris, 1835, iv.

Monsarrat, K. W.—"Mammary Cancer." Discussion at Med. Soc. of London (Liverpool), *Brit. Med. Jour.*, 1902, i, p. 272.

Monsarrat, K. W., and Williams, Idwal J.—"Intramural Extension in Rectal Cancer," *The Lancet,* Lond., 1913, ii, p. 1546.

Monsarrat, K. W., and Williams, Idwal J.—"Intramural Extension in Rectal Cancer," *Brit. Jour. of Surg.*, 1913, i, p. 173.

Morestin, H.—"Le cancer de la joue," XIII Cong. Int. de Méd., Paris, 1900, Vol. X, p. 264 (Chir. gén.).

Packard, John H.—"Three Cases of Intra-Thoracic Tumor—Cystic Substernal Goitre—Sarcoma of Anterior Mediastinum—Primary Endothelium of Pleura," *Univ. Med. Mag.*, Phila., 1895-6, viii, 605-698, 1 pl.

Pilz, C. O.—"De arteriæ carotidis utriusque ligatura," Berlin, 1865.

Paine, Alexander, and Nicholson, G. W.—"Surgical Interference in Cancer," *Brit. Med. Jour.,* July 22, 1911, Vol. 2, p. 153.

Pryor, W. R.—"The Surgical Anatomy of the Internal Iliac Artery in Women, and a More Radical Operation for Malignant Disease of the Uterus," *Am. Jour. Obst.,* N. Y., 1896, xxxiii, 801-817, 1 pl.

Rodman, W. L.—"Cancer of the Breast," *Jour. Am. Med. Assn.,* May 22, 1909, lii, p. 1648.

Rodman, William L.—"The Early Diagnosis of Cancer of the Breast and Best Operative Technic," *Penn. Med. Jour.*, 1909, Vol. XIII, No. 2, p. 100.

Rouville et Martin.—"Tumeur mixte de la parotide d'un volume remarquable," Bull. et Mém. Soc. anat. de Paris, 1904, lxxix, 659.

Roux.—"Tumeur fangueuse sanguine intra-osseuse; ligature de l'arteria brachiale," *Gaz. d. Hôp.,* Par., 1830-31, vi, 116.

Roux, G.—"Aneurysme cirsoïde de la région temporale droite; dilatations nombreuses et volumineuses des artères de la face et du crâne du même coté; ablation de la tumeur précédé de la ligature de la carotide externe; guérison," *Marseille méd.*, 1897, xxxiv, p. 481, 493.

Rowntree, Cecil.—"Tumors," in "A System of Treatment." Edited by A. Latham and T. Crisp English, Vol. I, p. 135.

Ryall, C.—"Cancer Infection and Cancer Recurrences: A Danger to Avoid in Cancer Operations," *The Lancet,* Lond., 1907, ii, 1311-1316.

Ryall, C.—"A Lecture on the Treatment of Advanced Uterine Carcinoma and Ligation of the Internal Arteries," *Chir. Jour.*, Lond., 1911-12, xxxix, 273-276.

Stiles, Harold Jalland.—"The Surgical Anatomy of the Breast and Axillary Lymphatic Glands considered, with reference to the morbid anatomy and treatment of carcinoma; with a note on the 'nitric acid method' of demonstration," Trans. Med. Chir. Soc., Edinb., 1891-2, n.s., xi, 37-70, 2 pls.; also, *Edinb. Med. Jour.,* 1892-3, xxxviii, 26.

Stiles, Harold Jalland.—"On the Dissemination of Cancer of the Breast," *Brit. Med. Jour.*, 1899, Vol. I, p. 1452.

Stiles, Harold Jalland.—"Carcinoma of the Mamma," *Brit. Med. Jour.,* 1892, ii, p. 673.

Stiles.—"Clinical Report of a Case of Cavernous Lymphangioma of the Subcutaneous Tissue of the Forearm" (under care of Professor Chiene), Edinburgh Hosp. Rep., 1893, i, 520-534, 3 pls.

Stiles, Harold Jalland.—"On the Dissemination of Cancer of the Breast," *Brit. Med. Jour.*, 1899, Vol. I, p. 1453.

Tavel, E.—"Ueber die subkutane Drainage des Aszites," *Correspondenz-Blatt f. Schweiz. Aerzte,* Basel, 1911, xli, 806-810.

Theilhaber, A.—"Die Verhütung der Recidiven nach Krebsbehandlung," *Deutsch. Ztschr. f. Chir.*, Leipz., 1913, cxxv, 193-208.

Travers, B.—"A Case of Aneurism by Anastomosis in the Orbit, Cured by the Ligation of the Common Carotid Artery," Med. Chir. Trans., London, 1817, ii, 3d ed., 1-16; also, transl. in *Jour. d. prakt. Heilk.*, Berl., 1814, xxxviii, 3 s., 38-56; also, "Case of Wounds of the External Carotid Artery, Behind the Angle of the Jaw, for Which the Common Carotid Artery Was Tied," *London Med. and Phys. Jour.*, 1826, n.s., l, 331-339; also, *Lancet*, 1826, x, 572-575.

Treves, Sir Frederic.—"A Case of Sarcoma of the Buttock Treated by Ligature of the Internal Iliac Artery," Clin. Soc. of London. Reported in the *Lancet*, Lond., June 4, 1892, p. 1244.

Tricomi, Ernesto.—"Ligation Operation in Resection of the Liver." Case reported in *Lancet*, Lond., May 19, 1894, p. 1262.

Tuffier.—"Essai sur les ligatures vasculaires dans les tumeurs inopérables et dans certaines infections," Assoc. franç. de Chir., II Cong. de Chir., Paris, 1897, p. 192.

Tyzzer, E. E.—"Factors in the Production and Growth of Tumor Metastasis," *Jour. of Med. Research*, 1913, n.s., xxiii, p. 309.

Walther, M.—"Néoplasme du pylore à type de limite plastique—Tumeurs des deux ovaires et de l'utérus de même nature," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, iii, 268-280.

Walther, M.—"De la résection des muscles dans l'ablation du cancer du sein," Bull. de l'assoc. franç. pour l'étude du cancer, 1910, iii. 92-104.

Wherry, George.—"A Successful Case of Intraperitoneal Ligation of the Internal Iliac Artery," *The Lancet*, Lond., July 15, 1893, p. 136.

Wyeth, John A.—"The Surgical Anatomy of the Carotid Arteries, as Deduced from One Hundred and Three Consecutive Dissections." New York, 1876.

Wyeth, John A.—"The Surgical Anatomy and History of the Common, External and Internal Carotid Arteries." Prize Essay. Trans. Am. Med. Assn., 1878, Vol. XXIX, p. 9.

Wyman, H. C.—"Ligation of Splenic Artery for Cure of Hypertrophy of Spleen," *Jour. Am. Med. Assn.*, Chicago, 1889, xii, 764.

Zykow.—"Surgical Measures in Non-Operative Cancers of the Uterus," *Russky Vrach*, St. Petersb., 1905, iv, 1115-1117.

IRREMOVABLE AND INOPERABLE CANCER

(SEE ALSO SURGICAL AND NON-SURGICAL TREATMENT)

Bainbridge, W. S.—"Irremovable Cancer," *New York Med. Jour.*, Oct. 3, 1908, p. 625.

Beatson, Sir G. T.—"The Treatment of Inoperable Cancer." Discussion at the 70th Annual Meeting of the British Medical Association, Manchester, Section of Surgery, *Brit. Med. Jour.*, Oct. 25, 1902, pp. 1293, 1297, 1298; also, "Inoperable Carcinoma of the Female Mamma," *Glasgow Med. Jour.*, 1911, n.s., lxxvi, p. 85.

Beatson, Sir G. T.—"On the Treatment of Inoperable Cases of Carcinoma of the Mamma—Suggestions for a New Method of Treatment, with Illustrative Cases," *The Lancet*, Lond., July 11, 1896, pp. 104, 162.

Beck, J. C.—"Experiments with the Autolytic Solutions in the Treatment of Inoperable Cancer of the Throat, Neck and Face," Trans. Am. Laryngol., Rhinol., and Otol. Soc., 1912, xviii, 475-479.

Coley, W. B.—"The Treatment of Inoperable Cancer," *The Practitioner*, Lond., 1899, Vol. LX, n.s., p. 497.

Daniel, C.—"The Diagnosis and Treatment of Inoperable Cancer," *Interstate Med. Jour.*, St. Louis, 1913, xx, 1001-1015.

Gould, Sir Alfred Pearce.—"The Bradshaw Lecture on Cancer," 1910, ii, p. 1664.

Gould, Sir Alfred Pearce.—The Purvis lecture on "The Treatment of Inoperable Cancer," *The Lancet*, Lond., Jan. 25, 1913, p. 215.

Lewin, C.—"Wie behandeln wir inoperable Geschwülste?" *Therap. d. Gegenw.*, Feb., 1913, n. s. 15, p. 71.

Morris (Sir) Henry.—"The Treatment of Inoperable Cancer," II Cong. soc. int. de chir., Brux., Sept. 21-25, 1908, Vol. II, pp. 295-318 (Reports); also, *The Lancet*, Lond., Oct. 3, 1908, Vol. II, p. 997.

Tuffier.—"Traitement du cancer inopérable," Paris, 1911; also, in *Œuvres Méd.-Chir.*, Dr. Gitzman, No. 63.

Warden, A. A.—"Radium and Inoperable Cancer," *Brit. Med. Jour.*, 1913, Vol. II, p. 1067.

INDEX OF AUTHORS

INDEX OF SUBJECTS

Printed in the United States of America.